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Retrieval of Autobiographical Memory in Alzheimer's Disease: Relation to Volumes of Medial Temporal Lobe and Other Structures

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ABSTRACT: The representation of autobiographical memory is distributed over a network of brain structures, with the medial temporal lobe (MTL) at its epicenter. Some believe that, over time, all memories become independent of their MTL component (''consolidation theories''). Others have suggested that this is true only of semantic memory, while episodic aspects of autobiographical memories are dependent on the MTL for as long as they exist, such as multiple trace theory (MTT). In the present study, the volumes of 28 brain regions, including the MTL, and their relation to autobiographical memory were investigated in a group of patients with Alzheimer's disease with varying degrees of retrograde memory loss as assessed by the Autobiographical Memory Interview (AMI). We used the multivariate analysis method of partial least squares (PLS) to assess patterns of atrophy that can lead to retrograde amnesia. We found that different aspects of autobiographical memory were associated with different patterns of tissue loss. Personal semantics were related to a pattern of bilateral anterior and posterior lateral temporal cortex degeneration, more pronounced on the left, as well as right frontal degeneration. Autobiographical event memory (''episodic'') was associated with combined atrophy in bilateral MTL and anterior lateral temporal neocortex, more pronounced on the right. This pattern was invariant for memories from childhood, early adulthood, and recent memories, in line with the predictions of MTT, suggesting that MTL tissue is crucial for retrieval of episodic memories regardless of their age. © 2005 Wiley-Liss, Inc.

KEY WORDS: retrograde amnesia; hippocampus; multiple trace theory; consolidation; partial least squares

INTRODUCTION

Little is known about the neural substrate and mechanisms of retrograde memory loss, although the phenomenon was first described clearly more than a century ago (Ribot, 1881). One reason for this relative lack of progress is the inherent difficulty in assessing retrograde memory performance when the history of exposure to events (i.e., the encoding stage) is unknown to the researcher. In recent years, there has been renewed interest in this important field of research. As in studies of anterograde memory, investigators have noted important distinctions between different types of retrograde memory, with relative sparing of one type accompanied by severe deficits in another. Most importantly, distinctions between semantic knowledge (e.g., vocabulary, public events, famous persons) and personal autobiographical memory have been noted (Tulving, 1972, 1983) and refined (Tulving, 2002; Wheeler et al., 1997). Semantic memory involves knowledge that is devoid of the context in which the information was acquired, whereas episodic memory involves recollection of context-rich autobiographical events with a distinct sense of personal re-experiencing. Additionally, dissociations within autobiographical memory, personal semantics, generic representations, and episodic re-experiencing of personal events have been described (Brewer, 1986; Burgess and Shallice, 1996; Conway, 2001; Conway and Pleydell-Pearce, 2000). These dissociations shed new light on a controversy regarding the role of medial temporal lobe (MTL) structures in retrieval of remote memory. Note, however, that semantic and episodic aspects of memory can also be affected simultaneously, although not necessarily to the same degree (Kopelman, 1989; Reed and Squire, 1998; Rempel-Clower et al., 1996). In the present study, we address this issue by examining the relationship between tissue loss in the MTL of patients suffering from Alzheimer's disease (AD) and retrograde memory loss of autobiographical memory for episodes and for semantic knowledge about oneself.

According to consolidation theories, structures within the MTL, particularly the hippocampus, but also surrounding parahippocampal, perirhinal, and entorhinal cortices, are crucial for the acquisition of new memories, and temporarily for their representation as MTL–neocortical ensembles (Alvarez and Squire, 1994; Hodges and McCarthy, 1995; Scoville and Milner, 1957; Squire, 1992; Squire and Alvarez, 1995). The process of consolidation acts to transform these memories into permanent stable representations within temporal neocortex, independent of the MTL

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component. This process is thought to apply to all types of declarative memory (Alvarez and Squire, 1994; Squire, 1992; Squire and Alvarez, 1995). Consequently, retrograde amnesia (RA) associated with damage restricted to MTL should be time-limited (Bayley et al., 2003), although the precise limits of consolidation have never been defined, and the process may require decades for completion in humans.

There is controversy, however, as to whether this process applies equally to all kinds of memory (i.e., semantic, personal semantic, personal episodic) or is characteristic only of certain types. In a review of the literature on retrograde amnesia, Nadel and Moscovitch (1997) noted a correspondence between the extent of MTL lesion and the extent of personal episodic memory loss. These investigators proposed an alternative to classical consolidation theory, called multiple trace theory (MTT), which suggests that different types of remote memory are differentially affected by damage to MTL structures (Fujii et al., 2000; Moscovitch and Nadel, 1998; Nadel et al., 2000; Rosenbaum et al., 2001). According to the MTT, semantic memories undergo a relatively brief period of consolidation, whereas episodic (or context-rich memories) depend on their hippocampal component for the duration of their existence.

The lesion evidence relevant to both consolidation theories and MTT is based primarily on analyses of lesion, and memory functioning in single-case studies (other lines of evidence are briefly reviewed in the Discussion). An alternative approach is to study a group of patients who have varying degrees of retrograde memory loss and to correlate their performance with their extent of loss of brain tissue, as reflected in volumetric analysis. To our knowledge, only one study to date has taken a group approach to examine the relationship between RA and MTL pathology, using volumetric measures (Kopelman et al., 2003), and another examined glucose metabolism at rest (Eustache et al., 2004). Kopelman et al. (2003) studied three groups of focal lesion patients (frontal lobe, diencephalic lobe, and temporal lobe), and measured the volumes of four brain structures (frontal lobe, thalamus, lateral temporal lobe, and MTL). In accordance with the predictions of MTT, MTL (hippocampus and parahippocampal region) volumes of the total group of patients were correlated with the scores for episodic incidents on the Autobiographical Memory Interview (AMI) (Kopelman et al., 1990), and inversely correlated with RA for news events. When specific groups were tested, the diencephalic amnesics showed very high correlations between RA and MTL volume on the AMI, possibly reflecting subtle but systematic changes in MTL volumes. By contrast, MTL volumes of the MTL patients only showed correlations with RA for news events. The latter result was interpreted as evidence against MTT, which predicts a correlation between extent of damage to the MTL and severity of autobiographical memory loss.

A positron emission tomography (PET) study of patients with dementia of the AD type found significant positive correlations between general autobiographical scores and metabolism in the right hippocampus for recent memories only, using a task similar to the AMI (Eustache et al., 2004). These investigators noted, however, that memories provided for remote time periods, were semantic, while only memories in the recent time period were episodic in nature. Thus, Eustache et al. (2004) rightly conclude that both MTT and consolidation theories would predict the lack of correlation between remote (semantic) memories and hippocampal glucose metabolism. That study did not use a separate score for episodic remote memories, for which MTT and consolidation theories make contradictory predictions.

The present study sought to explore the involvement of different brain structures, particularly the MTL, in the retrieval of remote episodic and semantic memories among persons with AD. Although AD patients display great variability with regard to the patterns of parenchyma loss, certain ones are common, and MTL structures are typically among the most affected regions, in particular, early during the course of the disease. Thus, the memory performance of people with AD is particularly relevant to the debate described above.

Neurofibrillary tangles and neuritic plaques, the hallmark of AD, appear in entorhinal and perirhinal cortices, even at the preclinical stages of AD (Braak and Braak, 1997; Price et al., 1991). During later stages of the disease, degenerative processes proceed to other MTL structures, primarily the hippocampus and the amygdala. Early stages of the disease may also involve degeneration in the frontal cortex, primarily the orbital frontal area (Van Hoesen et al., 2000; Van Hoesen and Solodkin, 1994). Importantly for the present study, several structural magnetic resonance imaging (MRI) studies have shown that reduced MTL volumes in AD are associated with these neuropathological changes. For example, antemortem MRI volumes correlate strongly with postmortem determined Braak and Braak neuropathological stage (Jack et al., 2002). Such correlations are true of both senile plaques and neurofibrillary tangles (Silbert et al., 2003). Thus, although not a critical assumption for the present report, there is a close relationship between MRI volumetrics and the functional status of tissue as defined by neuropathology in AD (for review, see Kantarci and Jack, 2003; for different findings in temporal lobe epilepsy, see Bothwell et al., 2001).

More importantly for the present report, MTL volume reduction in AD has been shown to be associated with deficits on both verbal and visual anterograde memory tests (e.g., Cahn et al., 1998; Deweer et al., 1995; Köhler et al., 1998a; Stout et al., 1999; Toledo-Morell et al., 2000). An association between anterograde memory and MTL volumes is even reported in mild cognitive impairment (MCI), a precursor of AD (Chételat et al., 2003). A recent meta-analysis (Van Petten, 2004) concluded that the vast majority of studies that examined older adults with degenerative diseases report significant correlations between MTL volumes and anterograde episodic memory (as opposed to studies of children, adolescents, and young adults, where the opposite pattern is common). However, the association of structural changes with retrograde memory performance has not been studied. By doing so, we hope to determine which regions, when damaged, lead to impaired remote autobiographical memory for episodes and personal semantics, and to bring this evidence to bear on theories of memory and consolidation.

TABLE 1.

*Performance on Selected Neuropsychological Tests**

Patient	MMSE	DRS	DRS_nm	NART_IQ	COWAT	CVLT1-5	CVLT-DR	VR1	VR2	WCSTcat
1	**25**	128	109	111.00	34	**12**	**0**	17	**0**	2
2	**24**	**115**	94	112.00	**17**	32	**6**	22	**0**	2
3	**21**	**114**	102	104.00	23	**18**	**0**	18	**0**	**1**
4	28	130	109	116.00	29	35	**2**	17	10	4
5	26	131	113	120.00	49	37	**1**	22	**0**	**2**
6	27	**120**	104	118.00	31	35	**3**	26	4	5
7	**21**	128	112	118.40	22	**19**	**1**	18	**0**	**0**
8	**21**	**100**	89	104.40	**14**	**13**	**0**	**6**	**0**	**1**
9	**20**	**111**	98	113.76	30	**14**	**0**	14	**0**	2
10	28	138	117	123.12	61	**17**	**0**	29	4	3
11	**22**	123	108	111.40	33	**16**	**0**	13	**1**	**0**
Average	23.91	121.64	105.00	113.83	31.18	22.55	1.18	18.36	1.73	2.00
SD	3.05	10.93	8.57	6.08	13.68	9.95	1.89	6.34	3.17	1.55

COWAT, Controlled Oral Word Association (FAS); CVLT 1–5, California Verbal Learning Test (total score trials 1–5); CVLT-DR, California Verbal Learning Test (Delayed Recall); DRS, Dementia Rating Scale; DRS_nm, Dementia Rating Scale (no memory subscale); MMSE, Mini Mental State Examination; NART, National Adult Reading Test; VR1, Wechsler Memory Scale III immediate Visual Reproduction; VR2, Wechsler Memory Scale III delayed Visual Reproduction; WCSTcat, Wisconsin Card Sorting Test (number of categories achieved).

*Bold score represents significant deficit ($P < 0.05$) compared with the test's normative data, where available.

METHODS

Participants

The participants in this study were 11 mild dementia patients, with a diagnosis of probable AD-type dementia, using the National Institute of Neurological Disorders and Stroke–AD and Related Disorders (NINCDS–ADRDA) criteria (McKhann et al., 1984). The average duration between the time of first diagnosis and the present investigation was 2.25 (SD = 1.6) years. The patients (8 males; 10 right-handed; mean age = 75.3 ± 4.5; mean education = 14.82 ± 3.3) had an average Mini Mental State Examination (MMSE) of 23.9 ± 3.05 and estimated IQ based on the National Adult Reading Test (NART) of 114 ± 6.1. Basic neuropsychological test results for the participants are presented in Table 1. All patients gave written informed consent to participate in this study, which was approved by the ethics committee of Sunnybrook and Women's College Health Sciences Centre.

MRI Procedure

Magnetic resonance images (MRI) were acquired on a 1.5-T Signa scanner (GE Medical systems). Three image sets were acquired in the same imaging session: T1-weighted (an axial 3D SPGR with 5-ms TE, 35-ms TR, 1 NEX, 35° flip angle, 22 × 16.5-cm FOV, 0.859 × 0.859-mm in-plane resolution, and 1.2- to 1.4-mm slice thickness, depending on head size), proton density (PD), and a T2-weighted (interleaved axial spin echo with TEs of 30 and 80 ms, 3-s TR, 0.5 NEX, 20 × 20-cm FOV, 0.781 × 0.781-mm in-plane resolution, and 3-mm slice thickness).

Volumetrics

A three step in-house procedure was applied to the MRIs to obtain volumetric information. The first (brain extraction) and second (T1 segmentation) steps are an updated application of a previously published robust tissue segmentation procedure (Kovacevic et al., 2002). The third step (regional analysis) is an updated version of the parcellation procedure called Semi-Automatic Brain Region Extraction (SABRE) (Dade et al., 2004).

Tissue segmentation

Tissue segmentation was accomplished in two steps: brain extraction and T1 segmentation (Kovacevic et al., 2002). The brain extraction step involved an automatic segmentation algorithm that classified voxels into brain and nonbrain matter and a small amount of manual editing on the output mask. The updated procedure required a co-registration of the PD and T2- to the T1-weighted image in acquisition space. This update was implemented to minimize error related to mask rotation and to increase the amount of information available for manual editing. After the mask was applied to remove nonbrain matter from the T1-weighted image, a fully automatic histogram-based segmentation algorithm was applied. The algorithm used the means of four Gaussian curves to set local thresholds for the tissue classification of gray matter, white matter, and cerebrospinal fluid (CSF). For the present study, gray matter volumes were used for all the brain-behavior analyses.

Regional analysis

Regional analysis was accomplished using an updated application of the rapid and reliable SABRE method (Dade et al.,

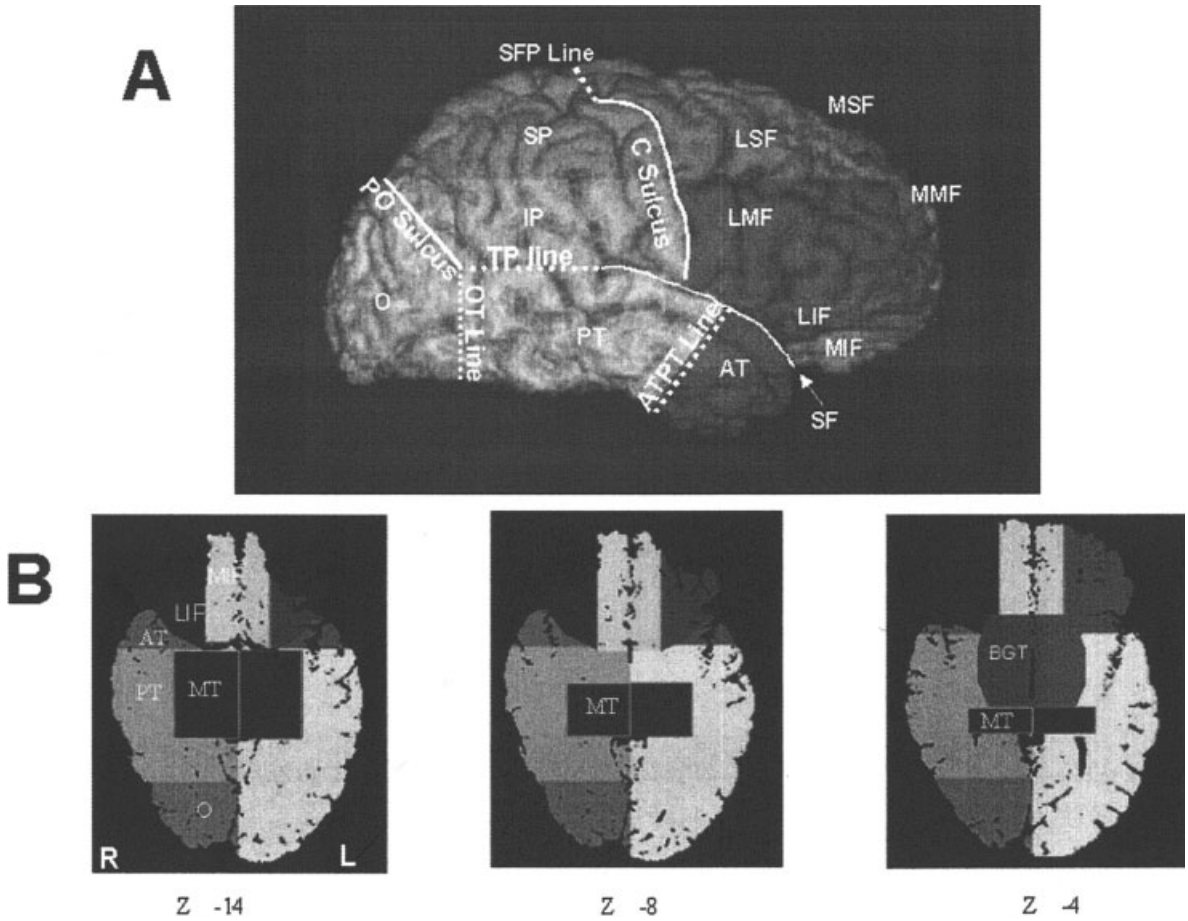

FIGURE 1. SABRE regional cortical divisions in lateral (A) and horizontal (B) views. Three axial views at horizontal divisions approximately equal to Talairach $z = 14$, $z = -8$, $z = -4$. LSF, lateral superior frontal; MSF, medial superior frontal; LMF, lateral middle frontal; MMF, medial middle frontal; LIF, lateral ventral frontal; MIF, medial ventral frontal; SP, superior parietal; IP, inferior parietal; O, occipital; AT, anterior temporal; MT, medial temporal; PT, posterior temporal; BGT, basal ganglia and thalamus; X, sagittal coordinate in Talairach space; C Sulcus, central sulcus; PO sulcus, parieto-occipital sulcus; SF, Sylvian fissure; SFP line, superior-frontal-parietal dividing line; ATPT line, division between anterior and poster temporal lobe; OT line, occipital-temporal dividing line.

2004), which combines manual and automatic approaches. This procedure required the user to input a few easily identified landmarks: central sulcus, Sylvian fissure, parieto-occipital sulcus, anterior commissure (AC), and posterior commissure (PC). From these individualized landmark inputs, a parcellation of 28 brain regions (Fig. 1) was derived using a predefined coordinate system. The landmark coordinates are combined with proportional Talairach-like grid coordinates to divide each individual's brain into 28 equivalent proportional cortical regions: 14 in the left hemisphere and 14 in the right. Proportional Talairach coordinates are used by SABRE to maintain the individual shape variability and correct for differences in intracranial capacity, while maintaining conformity to the standardized Talairach space. These coordinates are created for each individual's AC–PC-aligned image. The divisions, shown in Figure 1, include lateral and medial superior frontal, lateral and medial middle frontal, lateral and medial inferior frontal, superior parietal, inferior parietal, occipital, anterior lateral temporal, medial temporal, posterior lateral temporal, and anterior and posterior basal ganglia and thalamus. The precise boundaries and landmarks that delineate each region are provided in detail in Dade et al. (2004) and are represented in Figure 1. Because of the focus of the present study on temporal lobe structures, a brief description of the boundaries of the anterior, posterior lateral, and medial temporal divisions is presented.

Temporal lobe

The temporal lobe is divided into three regions: anterior, posterior lateral, and medial (Fig. 1). The extent of the medial temporal lobe region was based initially on Talairach atlas coordinates, and boundaries were manually refined to encompass hippocampus, amygdala, parahippocampal, perirhinal, and entorhinal cortices in a series of test brains reported in Dade et al. (2004) to minimize regional misclassification of tissue due to individual variations in brain anatomy.

Lateral temporal lobe. The superior border of the temporal lobe is defined by the Sylvian fissure and the temporal-parietal line. The anterior border is the inferior frontal demarcation, which was defined using four angled line segments extending

from midline to the outer edge of the brain. The placement of these lines was confirmed in the series of test brains, and the angles of these lines vary incrementally at seven specified *z* levels between AC–PC (0) and AC–PC (−2.5). The division between the anterior temporal and posterior temporal cortex starts at the midpoint between AC and PC at the bottom of the temporal lobe upward to a point at AC–PC (0), which is 0.5 of a gridline division anteriorly to the AC. The line continues upward until it intersects with the Sylvian fissure (open dots, Fig. 1).

Medial temporal lobe. The MTL region begins in the inferior temporal lobe near the ATPT line and progresses up through the posterior temporal region to the level of the basal ganglia and thalamus. The MTL extends sagittally from midline (M) to M(+/−2 sagittal grid divisions). The superior– inferior boundaries are at AC–PC to AC–PC (−4). At the most inferior level (AC–PC), the anteroposterior extent is 2.5 gridlines from (+0.5) to (−2) from the AC. From here, the region is moved smoothly up and back through the MT, such that the anteroposterior extent at the most superior level (AC–PC [−4]) is from 1.5 gridlines.

The SABRE parcellation is combined with the T1 tissue segmentation to produce measures of gray matter, white matter ventricular CSF, and sulcul/subdural CSF for each SABRE brain region. This was previously performed with the T1 segmentation aligned along the plane passing through the AC and PC (AC–PC plane). The updated version required a co-registration of the SABRE parcellation with the T1 segmentation before combining them (i.e., combination was performed in T1 acquisition space, not in AC–PC space). This update was implemented to prepare for the integration of a lesion segmentation procedure, and to avoid the problems associated with the rotation of the T1 segmentation along the AC–PC plane.

Previous research (Dade et al., 2004) has shown that the inter-rater reliability for this method is high, with all reliability coefficients ranging between 0.95 and 0.99 for the different regions. Construct validity investigation of the SABRE-derived volumetric data from healthy young and older adults showed significant differences in multiple brain regions in keeping with regional atrophy described in the literature by researchers using manual tracing methods (Dade et al., 2004).

There is no "gold standard" in brain volumetry, and the choice of method depends on the particular aims of each study. For the present study, SABRE was used because it was important to have whole brain measurements to demonstrate the specificity of association between different brain regions and behavior in the context of dementia. In semi-automated and automated methods of brain volumetry there is a tradeoff between sensitivity and reliability of any particular measure. Tisserand et al. (2002) showed that automated approaches cannot accurately reproduce smaller ROIs as defined by manual tracing. Smaller volumes tend to be less reliable because of individual differences, particularly in neocortical regions. In contrast, manual methods sometimes suffer from poor inter-rater reliability, particularly in regions with ill-defined anatomical borders. SABRE is a compromise between fully automated and manual approaches. The use of easily identified landmarks combined with automatic parcellation allows for highly reliable and reproducible volumetry on the one hand, and preservation of major individual differences on the other. Importantly, the use of proportional rather than absolute Talairach grid that is commonly used (e.g., Subramaniam et al., 1997; Tisserand et al., 2002) further enhances the fidelity of resultant brain volumes to the individual neuroanatomy. Voxel-based procedures also offer unbiased and reliable techniques for analysis. However, we chose to use SABRE because it does not require warping and smoothing procedures for co-registration to standardized maps, which are based on a younger population. Given that SABRE creates parcellations based on each individual's respective anatomical landmarks, we felt that it would be more appropriate for the purposes of this study of elderly persons with dementia.

No method of brain morphology is perfect. All methods, including our own, have their advantages and disadvantages. We believe SABRE represents a reasonable and cost-effective compromise that has been validated adequately (Dade et al., 2004).

Behavioral Measures

All participants underwent a standardized battery of neuropsychological tests that included, among others, the National Adult Reading Test (NART) (Nelson, 1982), Dementia Rating Scale (DRS) (Mattis, 1988), and California Verbal Learning Test (CVLT) (Delis et al., 1987). Table 1 presents the results of these tests, as well as other neuropsychological tests administered to the participants.

Autobiographical memory was tested using the AMI (Kopelman et al., 1990) according to the administration and scoring procedures described in the test manual. The AMI consists of two subscales (Personal Semantic and Autobiographical Incidents) and probes memory from three time periods: childhood (ages 0–18), early adulthood (ages 18–30), and recent (within the past 5 years).

The Personal Semantic subscale probes participants for information such as names of friends and teachers, locations of schools attended, home addresses, dates, and so forth. Each time period had a maximum score of 21 points. The Autobiographical Incidents subscale includes questions about specific events that occurred during each of the three time periods. Participants are required to provide temporal and spatial contextual information for each incident described in order to receive full credit. Three such incidents are probed for each time period, and specifications such as "first day at work" are used as probes. Each incident is scored out of a possible score of 3, based on the descriptive richness and specificity in time and place of the response following the manual. Because it has been suggested that such scoring may not be sufficiently sensitive for some purposes of testing autobiographical re-experiencing (Levine et al., 2002; Moscovitch et al., 2000; Piolino et al., 2002), we also counted the number of details provided by participants and used the total detail number as an additional measure of performance on specific event memory. We conducted the analyses (see below) using the scores from both scoring methods,

with no significant differences in the results obtained from the two methods. The scoring system from the test's manual is reported in the present study.

Multivariate Data Analysis

Multivariate analysis was performed using partial least squares (PLS) (McIntosh, 1999; McIntosh et al., 1996), using the brain volumes derived from the volumetric analysis and the scores from the AMI and neuropsychological assessment. PLS is a multivariate analysis technique that can be used to identify assemblies of brain region volumes that together covary in relation to behavioral measures. PLS identifies a new set of variables (called latent variables [LV]), that are similar in nature to principal components, through an analysis of the covariance between the volumes of all brain regions and the scores on different tests. The latent variables are those variables that optimally relate these two sets of measurements. Through the use of the multivariate technique of PLS, we were able to look at parenchyma loss in clusters of regions that commonly causes memory deficits in an exploratory way that is not biased by prior hypotheses regarding associations between particular regions and specific memory functions that were selected for each analysis (see below). This was particularly important for a population with dementia where damage preferentially affects certain brain regions, but is not restricted to them.

Four separate analyses were conducted. First, to identify specific collections of regions whose volumes relate to general aspects of autobiographical memory, PLS analyses were conducted using all brain volumes and the composite AMI scores (i.e., total scores derived from the test manual) on the Personal Semantic and Autobiographical Incidents subscales together. Second, to determine the specificity of the relationship of brain volumes to memory functioning, as opposed to general intellectual functioning, the AMI subscales and scores from the DRS, excluding the memory subscale, were used together in a separate PLS analysis. Third, to determine the relationship between retrograde autobiographical memory and anterograde memory functioning, the AMI subscale scores and a score for total learning on the CVLT were used in a third PLS analysis. Finally, to test the possible effect of remoteness of memories, PLS was implemented on the scores of each AMI subscale separately broken down by time period (childhood, early adulthood and recent). This analysis also allowed inspection of collections of brain regions that were uniquely associated with Event vs. Personal Semantic subscales. Thus, we combined a hypothesis testing approach reflected in the specific analyses performed with a hypothesis-free PLS analysis that did not presuppose specific regions within each analysis.

As a first step in the PLS analyses, correlations were computed between the regional summed gray matter volumes and the behavioral measures. Correlation maps were constructed and stacked to form a matrix and were analyzed with Singular Value Decomposition to produce mutually orthogonal latent variables, each comprised of a singular "volumetric image" and a singular behavioral profile. The numerical values ("salience") within the "volumetric image" are weighted linear combinations of brain volumes that covary with behavior, and may be positive or negative. They are similar in nature to factor loadings in factor analysis and reflect the contribution of individual brain volumes to the latent variable. Finally, the singular images were multiplied by the raw volume values to produce individual "brain scores" for each subject. Brain scores reflect the extent to which each subject expresses the pattern represented in the singular image. These brain scores were then correlated with behavioral scores to produce scan profiles, which are proportional to the singular profiles derived by Singular Value Decomposition and indicate the extent and direction to which a particular set of regions is associated with different behavioral measures (for details, see McIntosh, 1999).

The statistical significance of each latent variable as a whole was assessed by permutation tests (Edgington, 1980; McIntosh et al., 1996), with a corrected threshold of $P < 0.0125$ to account for the multiple analyses conducted in this study. The stability of each brain volume's contribution to the latent variable was determined through bootstrap resampling (Efron and Tibshirani, 1986; Sampson et al., 1989). Brain regions in the singular images were considered reliable if they had a ratio of salience to SE greater than 3, corresponding to 99% confidence limits (Köhler et al., 1998b,c; McIntosh et al., 1999; Sampson et al., 1989). Thus, the ratio of salience to SE derived from the bootstrap analyses (see Figures 2–6) reflects the consistency with which the salience of a particular region is manifested across subjects.

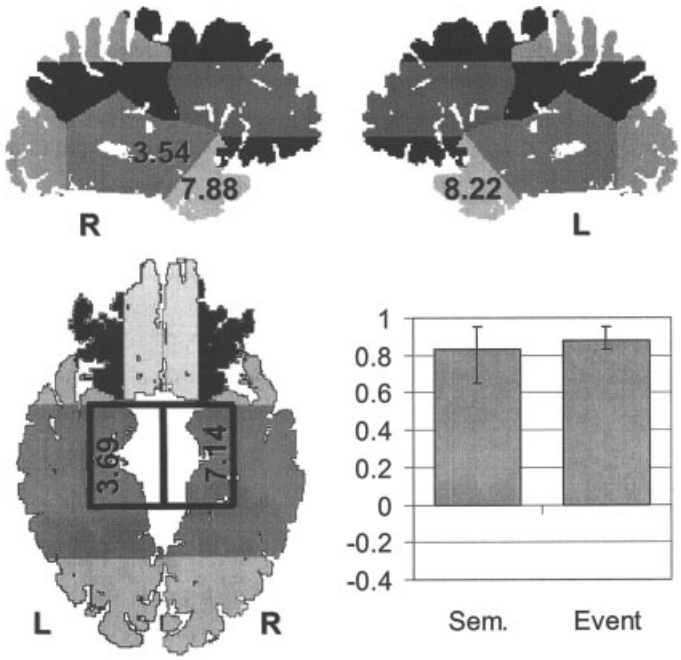

FIGURE 2. Latent variable 1 from PLS analysis of AMI composite scores and 28 regional brain volumes. The behavioral pattern associated with this latent variable is presented in the bottom right corner. Numbers on the schematic brain images represent the salience to SE ratios of regions that significantly contributed to the latent variable (i.e., bilateral MTL, bilateral anterior temporal and right lateral temporal cortex). Note that not all 28 regions are depicted in Figs. 2–6 and only significant saliences are denoted.

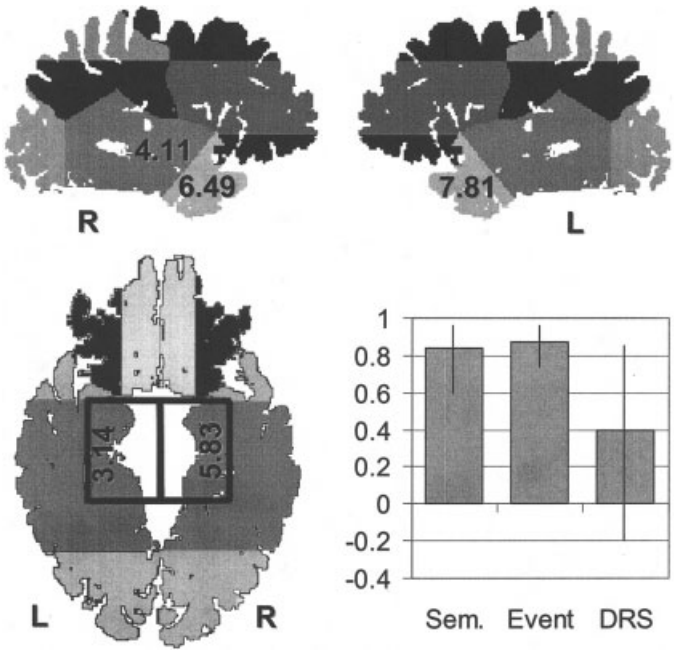

FIGURE 3. Latent variable 1 from PLS analysis of AMI composite scores, DRS and 28 regional brain volumes. The behavioral pattern associated with this latent variable is presented in the bottom right corner. Numbers on the schematic brain images represent the salience to SE ratios of regions that significantly contributed to the latent variable (i.e., bilateral MTL, bilateral anterior temporal and right lateral temporal cortex). Note that not all 28 regions are depicted in Figs. 2–6, and only significant saliences are denoted.

RESULTS

Behavioral Results

The performance of each patient and the group's mean are presented in Table 2. The overall averages on both schedules of the AMI resemble the results presented in the test's manual for a group of AD patients (see Kopelman, 1989) for the original data). There is a difference, however, between the scores obtained in the present study and those obtained by Kopelman (1989). For personal semantics, the average score for the recent time period in the present study was ~1 SD higher than that reported by Kopelman (1989), while early adulthood and childhood scores differed by <0.25 SD. Similarly, for recent event memory, our scores were ~0.6 SD higher than Kopelman's score, whereas the scores for early adulthood and childhood were closer to the ones reported by these authors (~0.2 SD lower). This pattern led to an overall flat gradient for both subscales compared with the gradient reported by Kopelman (1989), driven for the most part by better performance on recent memory in the present sample. These differences in the recent portions of the AMI may be associated with the severity of dementia, which was greater in Kopelman's sample. The deficits on recent recall in their sample likely reflect greater anterograde memory deficit. Importantly, some of our patients exhibited large impairments on one or both schedules, whereas others performed at normal levels, showing very little deficit or no deficit at all, a variability that facilitated the analysis of association between memory functioning and brain volume loss (see Kopelman et al., 1990 for normative data).

For six patients, we had a family member verify the responses independently. There were no significant inaccuracies in the patients' memories to warrant exclusion from the analyses. This finding is in agreement with that of Kopelman et al. (1990), who found few inaccuracies in the original study of the test, and also with Gilboa and Moscovitch (2002), who reviewed the literature on confabulation and noted that significant confabulation in AD only occurs late in the disease process.

Partial Least Squares

AMI composite scores

PLS analysis using the total scores from the two AMI subscales yielded one significant latent variable ($P = 0.01$), while the second latent variable failed to reach significance ($P = 0.06$). Regions associated with latent variable 1 included bilateral MTL and anterior temporal cortex (temporal poles), as well as the right lateral posterior temporal, all showing positive saliences (Fig. 2). This pattern was positively associated with both subscales; the correlation between patients' brain scores and the Personal Semantic scores was 0.83 (95% confidence

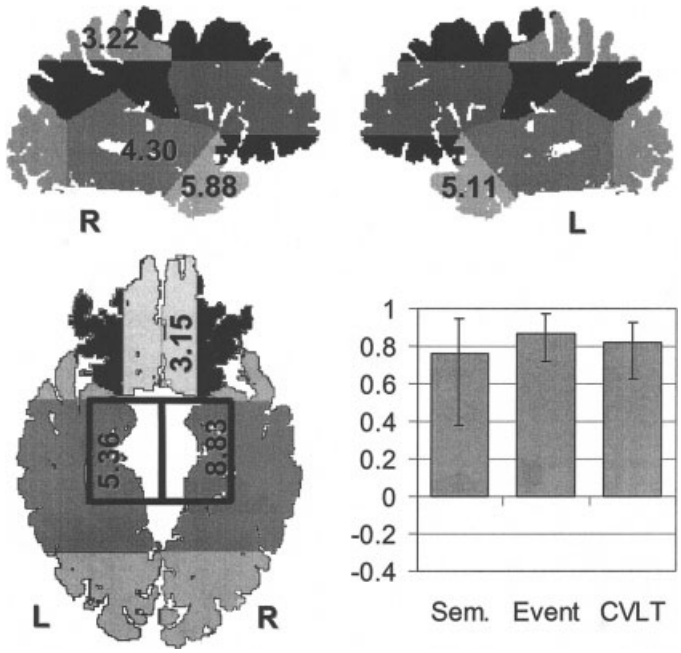

FIGURE 4. Latent variable 1 from PLS analysis of AMI composite scores, CVLT and 28 regional brain volumes. The behavioral pattern associated with this latent variable is presented in the bottom right corner. Numbers on the schematic brain images represent the salience to SE ratios of regions that contributed significantly to the latent variable (i.e., bilateral MTL, bilateral anterior temporal, and right lateral temporal, inferior medial frontal and superior parietal cortices). Note that not all 28 regions are depicted in Figs. 2–6, and only significant saliences are denoted.

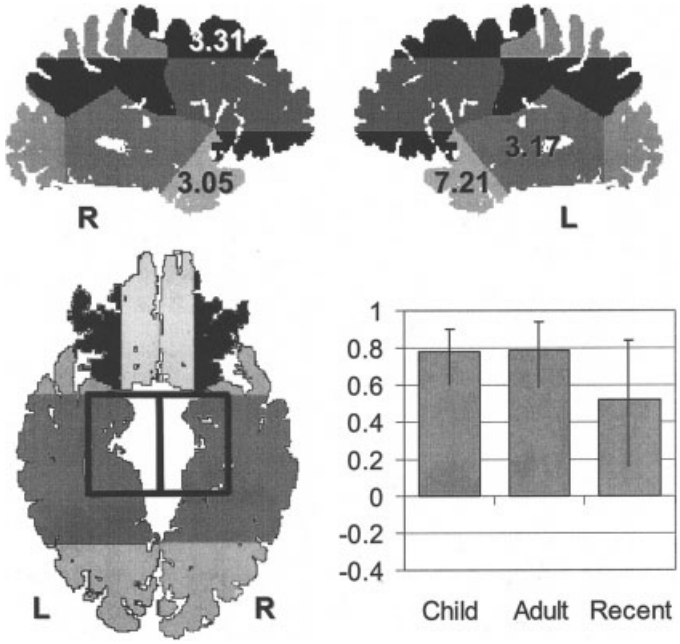

FIGURE 5. Latent variable 1 from PLS analysis of AMI Personal Semantic subscale, by age, and 28 regional brain volumes. The behavioral pattern associated with this latent variable is presented in the bottom right corner. Numbers on the schematic brain images represent the salience to SE ratios of regions that significantly contributed to the latent variable (i.e., bilateral anterior temporal, left lateral temporal, and right superior frontal cortex). Note that not all 28 regions are depicted in Figs. 2–6, and only significant saliences are denoted.

interval [CI]: 0.71–0.95); for event memory, it was 0.88 (CI: 0.81–0.95). Thus, the collection of regions within this latent variable represents a general pattern of parenchyma degeneration that, as a group, is associated with performance on autobiographical memory. Each individual region within this pattern may, however, be associated with different aspects of autobiographical memory (see below).

Latent variable 2, which failed to reach statistical significance, was positively associated with episodic memory and negatively associated with semantic memory. No specific region associated with this latent variable survived our cut-off from the bootstrapping test (ratio of salience to SE > 3). The only two regions that approached that cut-off were the left MTL (positive salience ratio of 2.11, i.e., positively associated with episodic memory) and the right frontal dorsomedial cortex (negative salience ratio of -2.05, i.e., associated with personal semantics). Although potentially interesting, latent variable 2 only accounted for 9.2% of the variance and thus will not be interpreted.

AMI and DRS

To test whether these patterns of covariances are specific to autobiographical memory or simply represent an association of general cognitive decline and brain atrophy, the total score on the Dementia Rating Scale (DRS) without its memory component was included in a PLS analysis with the AMI scores. Only one latent variable was significant (Fig. 3), which included the same regions as latent variable 1 in the analysis that was performed on AMI scores only. Both AMI subscales correlated positively with this latent variable, while the correlation of DRS total score was not significantly different from 0 (Fig. 3). This means that the pattern of brain-behavior covariances in this analysis was entirely driven by the memory scores, and that more general cognitive decline, as reflected in the DRS score, is not associated with this specific pattern of volume loss.

Personal semantic, autobiographical events, and CVLT

An analysis of the scores from the AMI and the CVLT total score revealed one significant latent variable ($P = 0.0001$). Latent variable 1 included bilateral MTL and bilateral anterior temporal lobe cortex, as well as right posterior temporal neocortex and the right superior parietal and ventromedial frontal regions (Fig. 4). This was associated with all three behavioral measures to the same extent, suggesting this collection of regions was important for retrograde and anterograde memory.

Personal semantic, autobiographical events, and the effect of age of memory

Only one latent variable was significant in each of the analyses when scores for different memory ages (rather than compo-

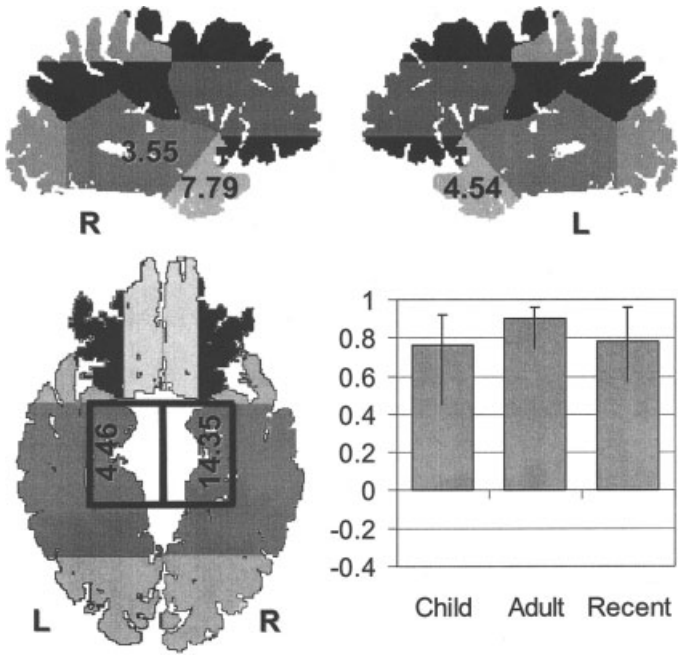

FIGURE 6. Latent variable 1 from PLS analysis of AMI Event Memory subscale, by age, and 28 regional brain volumes. The behavioral pattern associated with this latent variable is presented in the bottom right corner. Numbers on the schematic brain images represent the salience to SE ratios of regions that significantly contributed to the latent variable (i.e., bilateral MTL, bilateral anterior temporal and right lateral temporal cortex). Note that not all 28 regions are depicted in Figs. 2–6, and only significant saliences are denoted.

TABLE 2.

Scores on the Personal Semantic and Autobiographical Events schedules of the AMI

	Personal semantic memory				Event memory			
Patient	Childhood	Early adulthood	Recent	Total	Childhood	Early adulthood	Recent	Total
1	18	15	11.5	45	3	2	2	7
2	21	21	21	63	9	9	7	25
3	13	1.5	15	30	6	0	2	8
4	16.5	13.5	13.5	44	9	9	8	26
5	20	16.5	15	52	5	5	6	16
6	15	15.5	12	43	6	3	3	12
7	18	14	18	50	4	6	4	14
8	10	8	13	31	3	2	1	6
9	5.5	10.5	14	30	0	1	1	2
10	20	18	18.5	57	7	3	7	17
11	10	18.5	19	48	4	6	9	19
Average	15.18	13.82	15.5	44.5	5.09	4.18	4.54	13.81
SD	5	4.47	3.15	10.94	2.7	3.06	2.94	7.74

site scores) were included in the analysis of semantic ($P = 0.006$) and event memory ($P = 0.01$) subscales separately. There was no effect of remoteness of memories as indicated by the positive correlations of brain scores and latent variable scores on all ages both for the semantic (Fig. 5) and the event memory (Fig. 6) subscales of the AMI. [The analyses using the detail score of the AMI event memory subscale were very similar to those obtained from the standard scoring system. This may be related to the robustness of the correlations in the present study that are easily revealed under either crude or more refined scoring systems (for further details, see the Discussion).] The correlation of the score on recent personal semantics appears slightly lower than that of the more remote ones. Our clinical experience suggests that the items included in that scale (e.g., "Place where subject spent last Christmas"; "Date of arrival at this hospital") tap slightly different types of information than the earlier scales (e.g., "Name of high school"; "Name of subject's first child"). Nonetheless, the Personal Semantic subscale as a whole was associated with bilateral anterior and left posterior temporal neocortex, as well as right superior frontal lobe. Event memory was associated with bilateral MTL, bilateral anterior and right posterior temporal neocortex (Fig. 6). This suggests that the MTL saliences observed in the analyses of composite scores of the AMI were primarily driven by the event memory scores of the participants and is compatible with the trend of latent variable 2, which failed to reach significance.

All analyses were performed using gray matter volumes because gray matter volume changes have been found to be predictive of episodic memory performance in dementia patients (Petkov et al., 2004), as opposed to white matter hyperintensities, which were predictive of episodic memory performance only in healthy older adults. However, we also performed the analyses using white matter volumes. The overall pattern was very similar, in that event memory was associated with MTL and lateral temporal volumes, whereas memory for personal semantics was associated with lateral temporal white matter. The main difference was that memory for personal semantics was also associated with bilateral occipital white matter and both semantic and event memory were associated with left midfrontal white matter volumes (Appendix 1).

Correlations

To demonstrate further the relationships between individual regions and performance on autobiographical memory, we computed Pearson correlations between all the brain region volumes and scores on the AMI, DRS total (without the memory component), and CVLT. Partial correlations were computed, controlling for the effect of age. [Correlations of MTL volumes and age, as well as age and AMI and neuropsychological tests separately were not significant. This may be related to the fact that the only correlation that approached significance was a negative correlation between MMSE and age ($r = -0.66$), which suggests our younger subjects may have been somewhat more compromised.] The small N preclude correction for multiple comparison in this analysis; however, the reliability of the contribution of individual brain regions was assessed in PLS using a nonparametric bootstrap resampling method, attesting to the statistical significance of the findings. The correlations are presented for illustrative purposes only, as they are more readily understood by most readers. Appendix 2 presents these correlations; statistically significant correlations ($P < 0.01$, uncorrected) out of the 28 brain regions measured are flagged. The correlations revealed the same tendency for right hemisphere structures to be associated more with event memory measures, in particular between right MTL and event memory

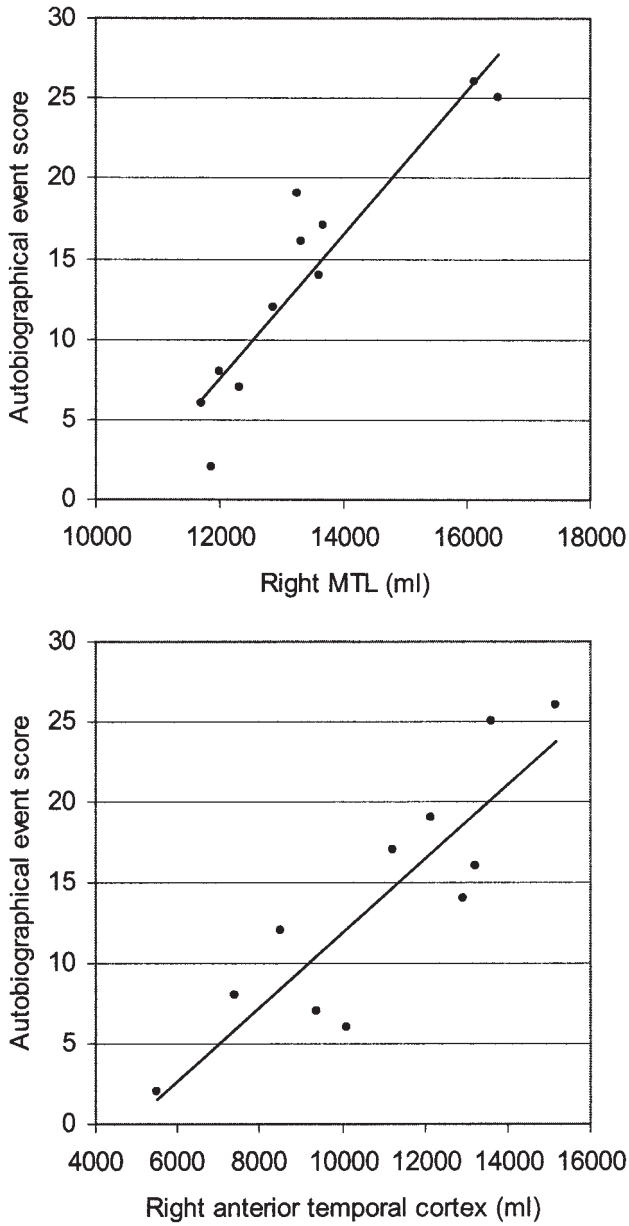

FIGURE 7. Correlations of Event memory scores from the AMI with right MTL and right anterior lateral cortex.

for all three age periods and for the total score. Figure 7 presents a scattergram for autobiographical event total score against right MTL volume and right lateral temporal cortex. [Removal of the two highest scores on event memory did not change the overall magnitude of the correlation (from $r = 0.93$ to $r = 0.91$), suggesting that the effect is robust and not the result of spurious scores.] CVLT correlated with volumes of medial prefrontal cortex.

Correlations of left hemispheric structures with AMI, DRS and CVLT behavioral measures (Appendix 2), revealed an association between anterior lateral temporal cortex and Personal Semantic scores (Fig. 8) and between CVLT and inferior frontal cortex volume. Event memory scores showed trends toward a correlation with MTL (e.g., total score on event memory with left MTL: $r = 0.71$, $P < 0.02$). It is also noteworthy that in addition to correlations of the CVLT with right and left frontal structures, it also showed a trend toward a correlation with left MTL volume ($r = 0.72$, $P < 0.02$), but no such trend was observed for right MTL. DRS scores, by contrast, did not correlate (or showed a trend toward correlation) with any of the specific brain volumes.

DISCUSSION

The results of the present study show three primary patterns: (1) a consistent and time-invariant association between the amount of tissue loss from the medial temporal lobe and the severity of retrograde memory loss for autobiographical events in a group of mild AD patients; (2) a consistent and time-invariant association between atrophy of lateral temporal cortex, stronger for the anterior portion (temporal pole) for both autobiographical event memory and personal semantics; and (3) a laterality effect, in which autobiographical event memory is associated more with right-sided structural volumes, while personal semantics are more strongly associated with left-sided volumes.

Remote Autobiographical Event Memory

The results of the present study show that the amount of tissue loss from anterior temporal neocortex and medial temporal lobe structures is strongly related to the extent of deficit in memory for autobiographical incidents. This association is maintained even when the contribution of the MTL to memory performance on the event subscale of the AMI was exam-

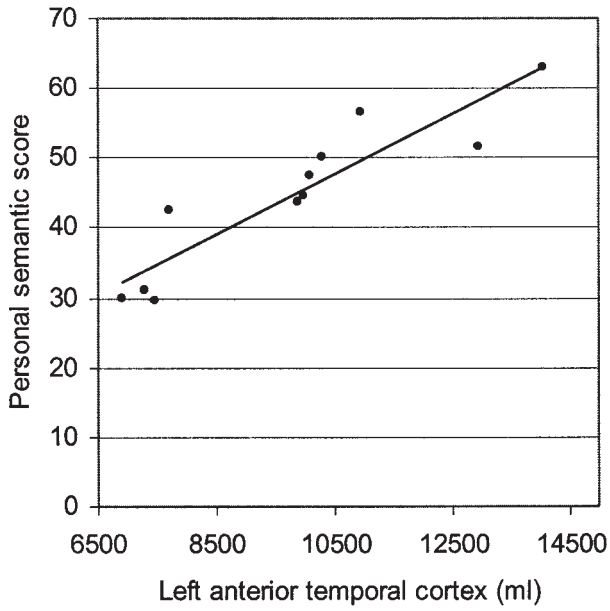

FIGURE 8. Correlations of Personal Semantic memory scores from the AMI with left anterior lateral temporal cortex.

ined in an analysis that included all the other regions with no a priori assumptions, using the multivariate analysis PLS. This is particularly important in the present study, as degeneration in AD may affect many different brain regions that could potentially be responsible for behavioral deficits in autobiographical memory. The use of SABRE to perform the volumetric analysis allowed us to study the combined effect of all brain regions on memory, and the strong association between MTL volumes and event memory despite the relatively crude measure of parenchyma loss, attests to the robustness of this relationship.

This pattern is highly consistent with the predictions of multiple trace theory (MTT), which posits that context-rich (episodic) memories depend on MTL–neocortical ensembles, whereas remote semantic memory is represented in the neocortex, independent of the MTL (Moscovitch and Nadel, 1998; Nadel and Moscovitch, 1997; Rosenbaum et al., 2001). Presumably, one would expect recent personal semantics to be associated with MTL volumes as well, by the predictions of MTT. However, the personal semantics probed by the AMI do not reflect only information recently acquired, as much of that information may remain unchanged for many years before the time of testing (e.g., one's address, names of neighbors, friends), so it is difficult to assess this prediction of MTT with the AMI.

The results are more difficult to accommodate within the framework of traditional consolidation theories. Such theories would not predict differential patterns of association for semantic and remote episodic memories. According to one version of consolidation theory (Alvarez and Squire, 1994; Squire, 1992; Squire and Alvarez, 1995), all declarative memories are represented within the neocortex once consolidation is complete, which renders them independent of their initial MTL component. In the present study, however, memory scores for childhood, early adulthood, and recent time were all associated to the same degree with volumes of the MTL. The results nicely complement those of Eustache et al. (2004), who used PET to assess the relationship between glucose utilization and remote autobiographical memory. They, too, found an association between episodic memory and right MTL function in AD, an association that did not exist for remote personal semantic/generic memories. The present study used separate measures for semantic and episodic memory and structural integrity to demonstrate a time-invariant relationship between MTL and episodic memory.

Our results are also partially compatible with those of Kopelman et al. (2003), who reported significant correlations between MTL volumes and scores on the incident schedule of the AMI for a group of 40 patients with amnesia following frontal, diencephalic or MTL lesions. Interestingly, when broken down by subgroup, significant correlations between MTL volumes and autobiographical incident memory score were found for the diencephalic group, but not the MTL lesions group. Similarly, multiple regression analysis with all the volumes reported in that study (MTL, thalamic, frontal cortex) accounted for roughly 60% of the variance in memory performance in the diencephalic and frontal groups, but did not predict memory performance in the MTL group.

The finding of a significant 0.8 correlation between MTL measures and memory in the diencephalic group but no correlation in the MTL group is puzzling. One possible explanation for the lack of correlation is the inclusion of three distinct etiologies in the MTL group, namely, patients with Herpes encephalitis, patients with anoxia and a patient with TLE. Comparison of that study and ours is difficult because there are considerable differences between the studies with respect to methodology (manual tracing of the hippocampus vs. semi-automated volumetric measures), and patient populations (focal lesion vs. dementia). These potentially could account for the difference between our study and Kopelman and colleagues' finding of no correlation within the MTL group.

The basic tenet of MTT is that there is a correspondence between the amount of damage to the MTL and the severity and extent of retrograde episodic memory loss, but it was always emphasized that the MTL was not considered functionally homogeneous (Fujii et al., 2000; Moscovitch and Nadel, 1998; Nadel and Moscovitch, 1997; Nadel et al., 2000). For example, based on a review of the literature, these investigators concluded that damage to the hippocampus proper (CA fields and dentate gyrus) was not sufficient to produce any considerable retrograde memory loss. However, when the lesion incorporated the whole hippocampal formation (CA fields, dentate gyrus, and subicular area), it was accompanied by RA for autobiographical episodes that spanned a decade or even a lifetime. For example, subicular damage exists in two cases with extensive ungraded retrograde amnesia following damage that was restricted to the hippocampal complex as determined by MRI in one (Cipolotti et al., 2001) and neuropathology in the other (Chan et al., 2002) (see also patient W.H. in Rempel-Clower et al., 1996). By contrast, when damage is limited to the CA fields and perhaps dentate gyrus, RA is minimal (Rempel-Clower et al., 1996), although it remains to be determined whether more sensitive tests would not uncover substantial RA even in these cases. This could imply that either the subiculum is a crucial structure that if damaged can lead to severe ungraded RA, or that the hippocampus proper and subiculum together constitute a distinct functional entity that when damaged completely can cause extensive RA.

Interestingly, Aggleton and his colleagues have advanced precisely that hypothesis with regard to anterograde memory loss (Aggleton and Brown, 1999; Aggleton and Shaw, 1996). These investigators suggest that the subiculum, CA fields, and dentate gyrus, together with the fornix, mammillary bodies, and anterior thalamus, constitute the "extended hippocampal complex," which they consider one of two distinct functional subsystems, the other being entorhinal, perirhinal, parahippocampal subsystem. According to this conceptualization, the latter subsystem is sufficient to support familiarity judgments, while the extended hippocampal complex is cru-

cial for recollection. A complete destruction of any of the components of the extended hippocampal system would cause severe anterograde recollection deficit. Although they do not directly discuss retrograde amnesia, there could be a theoretically important correspondence between recollection in anterograde memory functions and context-rich memories in retrograde amnesia.

The present study lacks the anatomical specificity to examine this possibility, although an association between performance on anterograde tests episodic memory (CVLT) and remote autobiographical event memory was found. Further studies with focal lesion patients are needed to resolve this issue.

To conclude, the present study found support for the basic tenet of MTT, namely that a correspondence exists between remaining MTL tissue, as reflected by structural volume, and the severity of retrograde memory loss for event information. However, it is also noted that structural extent of the damage per se may not be the only predictor. As in other fields of neuropsychology, circumscribed lesions to functional subcomponents of the MTL may cause severe RA as long as the entire extent of the subsystem is damaged. Admittedly, MTT currently lacks a set of specific hypotheses with regard to the nature of representation of memory codes and their distribution across different functional subsystems in the MTL. Refinement of both imaging techniques and functional (behavioral) analysis will be needed to address these issues.

Remote Personal Semantic Memory

The second pattern found in the present study is that tissue loss in the lateral temporal cortex, particularly the anterior aspect, is associated with memory loss both for personal semantics and for personal events. The inferior, lateral and anterior temporal cortices are crucially involved in semantic processing (Squire, 1992). The precise nature of information representation in the temporal cortex is not well understood. The anterior temporal cortex has been implicated in such functions as naming unique individuals, naming landmarks, and so forth, which suggests these regions are involved with retrieval of unique information associated with a person or an object (Damasio et al., 1996; Grabowski et al., 2001; Tranel et al., 1997). It stands to reason that damage to these regions should produce deficits in retrieval of personal semantic information on the AMI, which involves retrieval of names of friends and family, home addresses, and other unique factual information about the self. Posterior temporal regions may be associated with representation of more general aspects of semantic memory, such as representation of object attributes, category-specific representations, and representation of visual form (Martin and Chao, 2001), which are not as crucial components of autobiographical event retrieval.

The association of memory for autobiographical events, both recent and remote, with the intactness of the temporal neocortex, is compatible with both MTT and consolidation theories. There is no disagreement that the representation of the content of memories, semantic and episodic, is supported by the neocortex. The question is whether such episodic representations become independent of any MTL component, as consolidation theories predict, or whether such a component is essential for binding together the different aspects of the activated network that together represents an episodic memory, as MTT predicts. The time-invariant covariance pattern of the present data, in which MTL volume and temporal neocortical volume both covary with memory for autobiographical events, while temporal neocortical and frontal volumes covary with personal semantic memory, is more compatible with MTT.

One issue that remains unresolved is the extent to which the memories conveyed in the event memory section of the AMI are truly episodic. One potential concern is that only highly rehearsed or "semanticized" memories are recounted from remote periods. The problem with measuring episodic memories is that the term reflects not only the content of the memory, but the type of consciousness associated with retrieval (Wheeler et al., 1997; Moscovitch, 1995, 2000). Attempts to measure the construct of episodic memory have focused on either subjective reports such as the remember/know paradigm (Gardiner, 2001; Tulving, 2002) and various rating scales (Addis et al., 2004; Gilboa et al., 2004; Ryan et al., 2001) or on measuring the richness of the retrieved memory as a correlate of participants' ability to relive the episode. The scoring system of the AMI partially reflects the latter approach, with points awarded for elaborate or embellished description of the event. Previous research, however, has shown that the categorical scoring system employed by the AMI may not be sensitive enough to capture deficits in episodic memory in some cases. More refined methods, such as counting details in the subject's report, have been proposed (Levine et al., 2002; Moscovitch et al., 2000; Piolino et al., 2002; but see Bayley et al., 2003). In the present study, both scoring methods, detailed and categorical, were employed, yielding identical results. The likely reason for the correspondence is that the range of performance and individual differences could be captured even by categorical measures. Indeed, the high correlations between AMI scores and brain volumes leave little room for improvement by other scoring systems. Furthermore, the administration of the AMI does not include a detailed probing procedure, as do other methods (Levine et al., 2002; Piolino et al., 2002), such that more subtle differences in the richness of available memories may be obscured by participants' narrative styles. More research is needed to resolve the challenge of measuring episodic memory, which would likely involve the use of elaborate probing jointly with elaborate scoring schemes and combined with subjective rating scales, such as Remember/Know judgments. In the present study, it appears that the scoring system of the AMI was sufficient to capture real differences in participants' recollective abilities.

Lateralization of Remote Autobiographical Event (Episodic) and Semantic Memory

Although the latent variables for both semantic and autobiographical event subscales were associated with bilateral volume, a laterality effect was observed. Personal Semantic scores were more strongly associated with left-sided volumes of the left anterior lateral temporal cortex and uniquely associated with the left (but not right) posterior lateral temporal neocortex. Event memory, in contrast, was more consistently associated with right-sided than left-sided MTL (bootstrap ratio more than three times in size). Event memory was also strongly correlated with anterior and posterior lateral temporal cortex on the right.

The issue of laterality of the temporal lobe with regard to the retention and retrieval of autobiographical memory is unresolved. Recently, Eutastache et al. (2004) reported an association between right MTL glucose metabolism and recent episodic autobiographical memories, compatible with the findings reported here. Lesion studies that have tested autobiographical memory in patients with lesions to the MTL have reported impairment after either left or right lesion (Bergin et al., 2000; Viskontas et al., 2000), right lateralized lesions (O'Connor et al., 1992; Kopelman et al., 1999), or left lateralized lesion (Barr et al., 1990; Leplow et al., 1997). In contrast, Eslinger (1998) found that left MTL lesions caused time-limited retrograde amnesia for autobiographical memory. Even extensive damage to the left temporal lobe did not cause temporally extensive loss of memory for autobiographical events, although it did affect personal semantic memory (for a similar report, see De Renzi et al., 1987). Bilateral MTL damage caused severe and extensive loss of episodic autobiographical memory. The present findings are in line with Eslinger's observations, particularly with regard to the association between left temporal neocortical damage and personal semantic deficits. However, with regard to autobiographical event memory, our findings point to the possibility of a more lateralized deficit. It is important to emphasize, however, that both semantic and event memory subscales were associated with bilateral volume reduction, the difference between them being one of degree.

One possible factor affecting laterality is the patients' age. Many neuroimaging studies of autobiographical memory have reported left lateralized hippocampal activation (Addis et al., 2004; Maguire and Mummery, 1999; Maguire et al., 2000; Ryan et al., 2001). This effect holds even when retrieval cues are nonverbal (Gilboa et al., 2004) and for tasks that focused on visuospatial imagery (Niki and Luo, 2002). However, Maguire and Frith (2003) have reported bilateral activation in older adults compared with younger adults when retrieving personal memories in response to a verbal cue. Thus, an interaction of age and parenchyma loss may be responsible for the lateralization trends observed in the present study with elderly patients and in the lesion studies mentioned above.

CONCLUSION

The present study found robust relationships between extent of remaining tissue, as reflected by MRI volumetry, and retrograde memory loss in a group of mild to moderate AD patients. Importantly, different types of memory were associated with different patterns of tissue volume. Personal semantic memory was related to a pattern of bilateral anterior and posterior lateral temporal cortex decline, more pronounced on the left, as well as right frontal. Autobiographical event memory was associated with combined volume in bilateral MTL and anterior lateral temporal neocortex. For event memory the association was stronger with remaining right-sided tissue, in accordance with some earlier reports but not others. Importantly, this pattern was not sensitive to the age of the memories tested, a finding that is in line with the predictions of MTT, suggesting MTL tissue is always involved in retrieval of episodic memories.

Acknowledgments

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APPENDIX

APPENDIX 1.

Ratios of Salience to SE From Bootstrap Associated With Different White Matter Brain Region Volumes of Latent Variable 1 From Analysis of Personal Semantic (Left) and Event Memory (Right) Subscales of AMI Broken by Age of the Memory

Region	Personal semantic (by age)	Event memory (by age)
Right MTL		6.77
Lateral anterior temporal	(2.9)[a]	5.74
Lateral posterior temporal	3.35	5.01
Occipital	4.39	—
Posterior basal ganglia/thalamus	—	3.91
Left MTL		3.91
Lateral anterior temporal	3.79	5.32
Lateral posterior temporal	5.25	—
Superior parietal	3.35	—
Occipital	5.0	—
Middle frontal	3.9	3.15

[a]Did not reach statistical criteria, but presented because of the similarity to the gray matter analysis that included this region.

APPENDIX 2.

Partial Correlations Between Right and Left Hemisphere Structures and Behavioral Measures (Controlling for Age)[†]

	AMI PS1	AMI PS2	AMI PS3	AMI PST	AMI EM1	AMI EM2	AMI EM3	AMI EMT	CVLT	DRS
Right hemisphere structure										
Sup. Fr.	0.69	0.28	0.60	0.54	0.14	−0.03	0.22	0.23	−0.12	0.23
Mid Fr.	0.42	0.35	−0.02	0.21	0.01	0.22	0.02	0.17	0.56	−0.14
Inf. Fr.	0.03	−0.26	−0.23	−0.18	0.37	0.08	0.12	0.21	0.70	0.03
Med. Sup. Fr.	0.69	0.43	0.28	0.60	0.09	0.26	0.07	0.16	−0.15	0.38
Med. Mid. Fr.	0.52	0.27	0.22	0.42	0.68	0.42	0.28	0.51	0.76*	−0.01
Med. Inf. Fr.	0.35	0.33	0.14	0.36	0.28	0.35	0.06	0.26	0.80**	−0.10
Sup. Parietal	0.25	0.25	0.21	0.30	0.51	0.58	0.49	0.60	0.69	0.24
Inf. Parietal	0.01	0.27	0.07	0.15	0.33	0.44	0.32	0.41	0.35	−0.13
Occipital	0.47	0.55	0.58	0.64	0.04	0.33	0.21	0.22	−0.03	0.41
Ant. BG/Thal.	0.57	0.25	0.01	0.38	0.20	−0.04	−0.06	0.03	0.36	0.01
Post. BG/Thal.	0.13	−0.44	0.04	−0.15	0.29	0.17	0.08	0.19	0.08	0.29
Lat. Ant. Temp.	0.61	0.55	0.55	0.70	0.63	0.92***	0.79**	0.88***	0.48	0.28
Lat. Post. Temp.	0.55	0.37	0.45	0.55	0.61	0.74	0.57	0.72	0.55	0.40
MTL	0.60	0.60	0.55	0.71	0.81**	0.92***	0.75*	0.93**	0.65	0.13
Left hemisphere structure										
Sup. Fr.	0.54	0.27	0.60	0.54	0.14	−0.03	0.22	0.12	−0.13	0.38
Mid Fr.	0.09	0.35	−0.02	0.21	0.01	0.22	0.02	0.10	0.35	0.10
Inf. Fr.	0.04	0.07	−0.27	−0.03	0.43	0.39	0.30	0.42	0.75*	0.16
Med. Sup. Fr.	0.65	0.34	0.02	0.46	−0.04	−0.11	−0.06	−0.05	−0.16	0.50
Med. Mid. Fr.	0.17	0.35	0.28	0.33	0.36	0.21	0.24	0.30	0.45	−0.11
Med. Inf. Fr.	−0.29	0.15	0.13	−0.02	−0.28	−0.23	−0.18	−0.26	0.17	−0.34
Sup. Parietal	0.21	0.53	0.41	0.47	0.16	0.46	0.27	0.34	0.27	−0.14
Inf. Parietal	0.17	0.23	0.18	0.24	0.53	0.59	0.63	0.66	0.55	0.13
Occipital	0.21	0.55	0.05	0.38	0.06	0.55	0.35	0.37	0.34	0.40
Ant. BG/Thal.	0.02	0.26	0.02	0.11	−0.20	−0.01	−0.02	−0.08	0.42	0.20
Post. BG/Thal.	−0.06	−0.42	0.22	−0.17	−0.01	−0.28	−0.25	−0.21	−0.16	−0.01
Lat. Ant. Temp.	0.81**	0.76*	0.67	0.92***	0.53	0.70	0.68	0.72	0.47	0.34
Lat. Post. Temp.	0.52	0.57	0.41	0.63	0.24	0.24	0.11	0.22	0.22	0.14
MTL	0.37	0.64	0.44	0.60	0.59	0.68	0.64	0.71	0.72	0.28

AMI, Autobiographical Memory Interview; PS1, Personal Semantic–Childhood; PS2, Personal Semantic–Early Adulthood; PS3, Personal Semantic–Recent; PST, Personal Semantic–Total; EM1, Event Memory–Childhood; EM2, Event Memory–Early Adulthood; EM3, Event Memory–Recent; EMT, Event Memory–Total; CVLT, California Verbal Learning Test; DRS, Dementia Rating Scale; Sup, Superior; Mid, Middle; Inf., inferior; Fr., frontal; Med., medial; Ant., anterior; Post., posterior; Lat., lateral; BG, basal ganglia; Thal., thalamus; MTL, medial temporal lobe.

[†]Number of significant correlations expected by chance at $P < 0.01$ is 2.8.

*$P < 0.01$. **$P < 0.005$. ***$P < 0.001$.

REFERENCES

Addis DR, Moscovitch M, Crawley AP, McAndrews MP. 2004. Recollective qualities, not temporal specificity, modulate hippocampal activation during autobiographical memory retrieval. Hippocampus 14:752–762.

Aggleton JP, Brown MW. 1999. Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. Behav Brain Sci 22:425–444.

Aggleton JP, Shaw C. 1996. Amnesia and recognition memory: a reanalysis of psychometric data. Neuropsychologia 34:51–62.

Alvarez P, Squire LR. 1994. Memory consolidation and the medial temporal lobe: a simple network model. Proc Natl Acad Sci USA 91:7041–7045.

Barr WB, Goldberg E, Wasswestein J, Novelly RA. 1990. Retrograde amnesia following unilateral temporal lobectomy. Neuropsychologia 28:243–255.

Bayley PJ, Hopkins RO, Squire LR. 2003. Successful recollection of remote autobiographical memories by amnesic patients with medial temporal lobe lesions. Neuron 38:135–144.

Bergin PS, Thompson PJ, Baxendale SA, Fish DR, Shorvon SD. 2000. Remote memory in epilepsy. Epilepsia 41:231–239.

Bothwell S, Meredith GE, Phillips J, Staunton H, Doherty C, Grigorenko E, Glazier S, Deadwyler SA, O'Donovan, CA, Farrell M. 2001. Neuronal hypertrophy in the neocortex of patients with temporal lobe epilepsy. J Neurosci 21:4789–4800.

Braak H, Braak E. 1997. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 18:351–357.

Brewer WF. 1986. What is autobiographical memory? In: Rubin DC, editor. Autobiographical memory. New York: Cambridge University Press.

Burgess PW, Shallice T. 1996. Confabulation and the control of recollection. Memory 4:359–411.

Cahn DA, Sullivan EV, Shear PK, Marsh L, Fama R, Lim KO, Yasavage JA, Tinkleberg JR, Pfefferbaum A. 1998. Structural MRI corre-

lates of recognition memory in Alzheimer's disease. J Int Neuropsychol Soc 4:106–114.
Chan D, Revesz T, Rudge P. 2002. Hippocampal, but not parahippocampal, damage in a case of dense retrograde amnesia: a pathological study. Neurosci Lett 329:61–64.
Chételat G, Desgranges B, de la Sayette V, Viader F, Berkouk K, Landeau B, Lalevee C, Le Doze F, Dupuy B, Hannequin D, Baron JC, Eustache F. 2003. Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. Brain 126:1955–1967.
Cipolotti L, Shallice T, Chan D, Fox N, Scahill R, Harrison G, Stevens J, Rudge P. 2001. Long-term retrograde amnesia . . . the crucial role of the hippocampus. Neuropsychologia 39:151–172.
Conway MA. 2001. Sensory-perceptual episodic memory and its context: autobiographical memory. Philos Trans R Soc Lond B Biol Sci 356:1375–1384.
Conway MA, Pleydell-Pearce CW. 2000. The construction of autobiographical memories in the self-memory system. Psychol Rev 107: 261–288.
Dade LA, Gao FQ, Kovacevic N, Roy P, Rockel C, O'Toole CM, Lobaugh NJ, Feinstein A, Levine B, Black SE. 2004. Semi-automatic brain region extraction (SABRE): a method of parcellating brain regions from structural magnetic resonance images. NeuroImage 22:1492–1502.
Damasio H, Grabowski TJ, Tranel D, Hichwa RD, Damasio AR. 1996. A neural basis for lexical retrieval. Nature 380:499–505.
Delis DC, Kramer JH, Kaplan EF, Ober BA. 1987. California Verbal Learning Test Form. II. San Antonio, TX: The Psychological Corporation.
De Renzi E, Liotti M, Nichelli P. 1987. Semantic amnesia with preservation of autobiographic memory. A case report. Cortex 23:575–597.
Deweer B, Lehericy S, Pillon B, Baulac M, Chiras J, Marsault C, Agid Y, Dubois B. 1995. Memory disorders in probable Alzheimer's disease: the role of hippocampal atrophy as shown with MRI. J Neurol Neurosurg Psychiatry 58:590–597.
Edgington ES. 1980. Randomization tests. New York: Marcel Dekker.
Efron B, Tibshirani R. 1986. Bootstrap methods for standard errors, confidence intervals and other measures of statistical accuracy. Stat Sci 1:54–77.
Eustache F, Piolino P, Giffard B, Viader F, De la Sayette V, Baron JC, Desgranges B. 2004. "In the course of time": a PET study of the cerebral substrates of autobiographical amnesia in Alzheimer's disease. Brain 127:1549–1560.
Fujii T, Moscovitch M, Nadel L. 2000. Consolidation, retrograde amnesia, and the temporal lobe. In: Boller F, Grafman J, editors. The handbook of neuropsychology. Vol 4. Amsterdam: Elsevier. p 223–250.
Gardiner JM. 2001. Episodic memory and autonoetic consciousness: a first-person approach. Philos Trans R Soc Lond B Biol Sci 356: 1351–1361.
Gilboa A, Moscovitch M. 2002. The cognitive neuroscience of confabulation: a review and a model. In: Baddeley AD, Kopelman MD, Wilson BA, editors. Handbook of memory disorders.2nd Ed. London: John Wiley & Sons. p 315–342.
Gilboa A, Winocur G, Grady CL, Hevenor SJ, Moscovitch M. 2004 Remembering our past: functional neuroanatomy of recollection of recent and very remote personal events. Cereb Cortex 14:1214–1225.
Grabowski TJ, Damasio H, Tranel D, Ponto LL, Hichwa RD, Damasio AR. 2001. A role for left temporal pole in the retrieval of words for unique entities. Hum Brain Mapp 13:199–212.
Hodges JR, McCarthy RA. 1995. Loss of remote memory: a cognitive neuropsychological perspective. Curr Opin Neurobiol 5:178–183.
Jack CR Jr, Dickson DW, Parisi JE, Xu YC, Cha RH, O'Brien PC, Edland SD, Smith GE, Boeve BF, Tangalos EG, Kokmen E, Petersen RC. 2002. Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. Neurology 58:750–757.
Kantarci K, Jack CR Jr. 2003. Neuroimaging in Alzheimer disease: an evidence-based review. Neuroimaging Clin North Am 13:197–209.
Köhler S, Black SE, Sinden M, Szekely C, Kidron D, Parker JL, Foster JK, Moscovitch M, Winocour G, Szalai JP, Bronskill MJ. 1998a. Memory impairments associated with hippocampal versus parahippocampal-gyrus atrophy: an MR volumetry study in Alzheimer's disease. Neuropsychologia 36:901–914.
Köhler S, McIntosh AR, Moscovitch M, Winocur G. 1998b. Functional interactions between the medial temporal lobes and posterior neocortex related to episodic memory retrieval. Cereb Cortex 8: 451–461.
Köhler S, Moscovitch M, Winocur G, Houle S, McIntosh AR. 1998c. Networks of domain-specific and general regions involved in episodic memory for spatial location and object identity. Neuropsychologia 36:129–142.
Kopelman MD. 1989. Remote and autobiographical memory, temporal context memory and frontal atrophy in Korsakoff and Alzheimer patients. Neuropsychologia 27:437–460.
Kopelman MD, Wilson BA, Baddeley AD. 1990. The autobiographical memory interview. Bury St. Edmonds: Thames Valley Test Company.
Kopelman MD, Stanhope N.Kingsley D. 1999. Retrograde amnesia in patients with diencephalic, temporal lobe or frontal lesions. Neuropsychologia 37:939–958.
Kopelman MD, Lasserson D, Kingsley DR, Bello F, Rush C, Stanhope N, Stevens TG, Goodman G, Buckman JR, Heilpern G, Kendall BE, Colchester AC. 2003. Retrograde amnesia and the volume of critical brain structures. Hippocampus 13:879–891.
Kovacevic N, Lobaugh NJ, Bronskill MJ, Levine B, Feinstein A, Black SE. 2002. A robust method for extraction and automatic segmentation of brain images. NeuroImage 17:1087–1100.
Leplow B, Dierks CH, Lehnung M, Kenkel S, Behrens C, Frank G, Mehdorn M. 1997. Remote memory in patients with acute brain injuries. Neuropsychologia 35:881–892.
Levine B, Svoboda E, Hay JF, Winocur G, Moscovitch M. 2002. Aging and autobiographical memory: dissociating episodic from semantic retrieval. Psychol Aging 17:677–689.
Maguire EA, Mummery CJ. 1999. Differential modulation of a common memory retrieval network revealed by positron emission tomography. Hippocampus 9:54–61.
Maguire EA, Mummery CJ, Buchel C. 2000. Patterns of hippocampal–cortical interaction dissociate temporal lobe memory subsystems. Hippocampus 10:475–482.
Martin A, Chao LL. 2001. Semantic memory and the brain: structure and processes. Curr Opin Neurobiol 11:194–201.
Mattis S. 1988. Dementia Rating Scale (DRS). Odessa, FL: Psychological Assessment Resources.
McIntosh AR. 1999. Mapping cognition to the brain through neural interactions. Memory 7:523–548.
McIntosh AR, Bookstein FL, Haxby JV, Grady CL. 1996. Spatial pattern analysis of functional brain images using partial least squares. NeuroImage 3:143–157.
McIntosh AR, Rajah MN, Lobaugh NJ. 1999. Interactions of prefrontal cortex in relation to awareness in sensory learning. Science 284:1531–1533.
McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS–ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34:939–944.
Moscovitch, M. 1995. Recovered consciousness: a hypothesis concerning modularity and episodic memory. J Clin Exp Neuropsychol 17: 276–290.
Moscovitch M. 2000. Theories of memory and consciousness. In: Tulving E, Craik FIM, editors. The Oxford handbook of memory. New York: Oxford University Press. p 609–625.
Moscovitch M, Nadel L. 1998. Consolidation and the hippocampal complex revisited. In: defense of the multiple-trace model. Curr Opin Neurobiol 8:297–300.

Moscovitch M, Yaschyshyn T, Ziegler M, Nadel L. 2000. Remote episodic memory and retrograde amnesia: was Endel Tulving right all along? In: Tulving E, editor. Memory, consciousness, and the brain: The Tallinn Conference. Philadelphia, PA: Psychology Press/Taylor & Francis. p 331–345.

Nadel L, Moscovitch M. 1997. Memory consolidation, retrograde amnesia and the hippocampal complex. Curr Opin Neurobiol 7: 217–227.

Nadel L, Samsonovich A, Ryan L, Moscovitch M. 2000. Multiple trace theory of human memory: computational, neuroimaging, and neuropsychological results. Hippocampus 10:352–368.

Nelson HE. 1982. The National Adult Reading Test (NART). Windsor, UK: NFER–Nelson.

Niki K, Luo J. 2002. An fMRI study on the time-limited role of the medial temporal lobe in long-term topographical autobiographic memory. J Cogn Neurosci 14:500–507.

O'Connor M, Butters N, Miliotis P, Eslinger P, Cermak LS. 1992. The dissociation of anterograde and retrograde amnesia in a patient with herpes encephalitis. J Clin Exp Neuropsychol 14:159–178.

Petkov CI, Wu CC, Eberling JL, Mungas D, Zrelak PA, Yonelinas AP, Haan MN, Jagust WJ 2004. Correlates of memory function in community-dwelling elderly: the importance of white matter hyperintensities. J Int Neuropsychol Soc 10:371–381.

Piolino P, Desgranges B, Benali K, Eustache F. 2002. Episodic and semantic remote autobiographical memory in aging. Memory 10: 239–257.

Price JL, Davis PB, Morris JC, White DL. 1991. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. Neurobiol Aging 12:295–312.

Reed JM, Squire LR. 1998. Retrograde amnesia for facts and events: findings from four new cases. J Neurosci 18:3943–3954.

Rempel-Clower NL, Zola SM, Squire LR, Amaral DG. 1996. Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. J Neurosci 16:5233–5255.

Ribot T. 1881. Diseases of memory. New York: Appleton.

Rosenbaum RS, Winocur G.Moscovitch M. 2001. New views on old memories: re-evaluating the role of the hippocampal complex. Behav Brain Res 127:183–197.

Ryan L, Nadel L, Keil K, Putnam K, Schnyer D, Trouard T, Moscovitch M. 2001. Hippocampal complex and retrieval of recent and very remote autobiographical memories: evidence from functional magnetic resonance imaging in neurologically intact people. Hippocampus 11:707–714.

Sampson PD, Streissguth AP, Barr HM, Bookstein FL. 1989. Neurobehavioral effects of prenatal alcohol. II. Partial least squares analysis. Neurotoxicol Teratol 11:477–491.

Scoville W, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. J Neurochem 20:11–21.

Silbert LC, Quinn JF, Moore MM, Corbridge E, Ball MJ, Murdoch G, Sexton G, Kaye JA. 2003. Changes in premorbid brain volume predict Alzheimer's disease pathology. Neurology 61:487–492.

Squire LR. 1992. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 99:195–231.

Squire LR, Alvarez P. 1995. Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr Opin Neurobiol 5: 169–177.

Stout JC, Bondi MW, Jernigan TL, Archibald SL, Delis DC, Salmon DP. 1999. Regional cerebral volume loss associated with verbal learning and memory in dementia of the Alzheimer type. Neuropsychology 13:188–197.

Tisserand DJ, Pruessner JC, Sanz Arigita EJ, van Boxtel MP, Evans AC, Jolles J, Uylings HB. 2002. Regional frontal cortical volumes decrease differentially in aging: an MRI study to compare volumetric approaches and voxel-based morphometry. NeuroImage 17: 657–669.

Toledo-Morrell L, Dickenson B, Sullivan MP, Spamovic C, Wilson R, Bennet DA. 2000. Hemispheric differences in hippocampal volume predict verbal and spatial memory performance in patients with Alzheimer's disease. Hippocampus 10:136–142.

Tranel D, Damasio H, Damasio AR. 1997 A neural basis for the retrieval of conceptual knowledge. Neuropsychologia 35:1319–1327.

Tulving E. 1972. Episodic and semantic memory. In: Tulving E, Donaldson W, editors. Organization of memory. New York: Academic Press.

Tulving E. 1983. Elements of episodic memory. Oxford: Clarendon Press.

Tulving E. 2002. Episodic memory: from mind to brain. Annu Rev Psychol 53:1–25.

Van Hoesen GW, Solodkin A. 1994. Cellular and system neuroanatomical changes in Alzheimer's disease. Ann NY Acad Sci 747:12–35.

Van Hoesen GW, Parvizi J, Chu CC. 2000. Orbitofrontal cortex pathology in Alzheimer's disease. Cereb Cortex 10:243–251.

Van Petten C. 2004. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia 42:1394–1413.

Viskontas IV, McAndrews MP, Moscovitch M. 2000. Remote episodic memory deficits in patients with unilateral temporal lobe epilepsy and excisions. J Neurosci 20:5853–5857.

Wheeler MA, Stuss DT, Tulving E. 1997. Toward a theory of episodic memory: the frontal lobes and autonoetic consciousness. Psychol Bull 121:331–354.