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Dissociations in Hippocampal and Frontal Contributions to Episodic Memory Performance

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Abstract

The hippocampus and frontal lobes both contribute to episodic memory performance. In the present study, the authors evaluated the relative contributions of hippocampus, frontal lobes, anterior temporal cortex, and posterior cortex to memory performance in neurodegenerative patients and normal older controls. Subjects (n = 42) were studied with structural MRI and a memory paradigm that measured delayed recall, semantic clustering during recall, recognition discriminability, and recognition response bias. Data were analyzed with multiple regression. Consistent with the authors' hypotheses, hippocampal volumes were the best predictor of delayed recall and recognition discriminability, whereas frontal volumes were the best predictor of semantic clustering and response bias. Smaller frontal volumes were associated with less semantic clustering during recall and a more liberal response bias. Results indicate that hippocampal and frontal contributions to episodic memory can be dissociated, with the hippocampus more important for memory accuracy, and frontal structures more important for strategic processing and decision making.

Keywords

memory; hippocampus; frontal lobes; organization; response bias

There is a general consensus that the hippocampus and adjacent structures are the primary anatomic substrate of episodic memory (Squire, 1998). The relationship between the hippocampus and memory has been borne out in numerous studies of patients with medial temporal damage due to surgery (Martin et al., 2002), vascular lesions (Ott & Saver, 1993), hypoxia (Yonelinas et al., 2002), Alzheimer's disease (AD; Jack et al., 1999; Kramer et al., 2004; Mungas et al., 2001; Petersen et al., 2000), and other conditions (Kopelman et al., 2001).

The frontal lobes also influence memory performance (Wheeler, Stuss, & Tulving, 1995). Although patients with frontal lobe lesions have a relatively well-preserved capacity to encode new information (Kopelman & Stanhope, 1997), memory performance can be affected because of deficits in executive skills such as planning and organization, response monitoring,

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inhibition of inappropriate responses, and memory for context (Kopelman, 2002). Deficits are often found on measures of free recall, delayed response, conditional learning, temporal order, autobiographical memory (Kopelman et al., 2003), and metamemory (Shimamura, 1995). Several investigators have suggested that frontal structures contribute to organizational aspects of memory at encoding and retrieval (Kapur et al., 1995; Moscovitch & Winocur, 1995; Tulving, Markowitsch, Kapur, Habib, & Houle, 1994) and thus are most evident on memory tasks that require active or strategic information processing (Petrides, 1995). For example, Alexander, Stuss, and Fansabedian (2003) reported that patients with focal frontal lesions exhibited poor implementation of subjective organization on a list-learning task. Incisa della Rocchetta and Milner (1993) also noted that the left frontal lobe is critical for strategic retrieval, and frontal structures help suppress potentially interfering items in verbal memory (Freedman & Cermak, 1986; Incisa della Rocchetta & Milner, 1993).

The neuroanatomical mediators of recognition memory have been less well studied. Some investigators have suggested that the hippocampus is critical for recognition memory (Gron et al., 2003; Grunwald et al., 2003; Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Reed & Squire, 1997), although some controversy remains (Aggleton & Shaw, 1996; Vargha-Khadem, Gadian, & Mishkin, 2001). The role of the frontal lobes in recognition memory is also unclear. Some aspects of recognition memory may be preserved in patients with frontal lobe damage (Janowsky, Shimamura, & Squire, 1989; Wheeler & Stuss, 2003). Other studies, however, have suggested that despite normal rates of recognition hits, frontal lobe injury may predispose toward making false-positive errors (Curran, Schacter, Norman, & Galluccio, 1997). Alexander et al. (2003) also showed that patients with left posterior dorsolateral lesions had a significantly elevated response bias that was associated with an increase in false-positive errors. This putative increase in response bias has been attributed to top-down controlled processes mediated by prefrontal cortex and may operate independently of memory accuracy (Swick & Knight, 1999).

Taken together, these studies suggest different contributions of hippocampal and frontal structures to human memory performance, with the hippocampus critical for consolidation and retention, and frontal structures important for strategic processing and decision making. However, several issues remain unresolved. Much of the clinical literature is based on between-groups comparisons with focal lesion patients and may not assess the potential contributions of multiple brain regions. Therefore, the overarching goal of this study was to use quantitative MRI to delineate the contribution of multiple brain regions to different components of episodic memory by taking advantage of the variance in regional brain volumes found in patients with neurodegenerative diseases. Specifically, we examined the MRI predictors of both recall and recognition memory. We hypothesized that hippocampal volumes would be selectively associated with level of memory accuracy in recall and recognition, whereas frontal volumes would be selectively associated with more strategic or decision-making aspects of recall and recognition.

Method

Subjects

A total of 42 subjects were enrolled. The sample consisted of 8 normal older controls, 13 subjects with AD, 11 with frontotemporal dementia (FTD), and 10 with semantic dementia (SD). The research diagnosis for each subject was made by a team consensus at the University of California, San Francisco Memory and Aging Center based on medical, social, and psychiatric history; neurological evaluation; extensive family interview; visual inspection of a brain image (CT or MRI); and mental status testing. The Neary criteria were used for the diagnosis of FTD and SD (Neary et al., 1998). Exclusionary features include early severe amnesia, early spatial disorientation, logoclonic speech, and myoclonus. The primary clinical

features in FTD are early decline in social and interpersonal conduct, early impairment in regulation of personal conduct, early emotional blunting, and early loss of insight. The primary clinical features of SD are a selective impairment of semantic memory; progressive, fluent, empty spontaneous speech; loss of word meaning; semantic paraphasias; anomia; and relative sparing of syntax and phonology. The National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984) were used for the diagnosis of probable AD. Demographic data of the subject groups are summarized in Table 1. There were no group differences in age or education; normal controls scored significantly higher on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975), but the three dementia groups were similar to one another.

Memory Assessment

Verbal episodic memory was evaluated with the California Verbal Learning Test–Short Form (CVLT-SF; Delis, Kramer, Kaplan, & Ober, 2000), a nine-item list presented over four learning trials, followed by 30-s delayed free recall, 10-min delayed free recall, 10-min delayed cued recall, and 10-min delayed recognition. The CVLT-SF affords assessment of several different aspects of verbal learning and memory pertinent to this study. We selected two variables that measured memory accuracy during recall and recognition. Delayed recall was assessed using a 10-min delayed free-recall trial. Because we were most interested in measuring delayed recall relative to immediate recall performance, we regressed delayed recall over the best immediate recall trial. Strategic processing during recall was assessed by quantifying semantic clustering (e.g., the tendency of subjects to organize the list on the basis of its semantic categories). The nine-item list was constructed using three words from each of three semantic categories (*clothing*, *fruits*, and *tools*) presented in an unclustered format. Because subjects are instructed to recall the words in any order, subjects can facilitate encoding and retrieval by consecutively recalled items belonging to the same semantic category. An index of semantic clustering was computed using previously described methods (Delis et al., 2000). First, the number of instances when subjects reported a correct word immediately after another correct word from the same semantic category was calculated. Second, the number of clustered items expected by chance was calculated using the number of categories represented on the target list as a correction factor (Stricker, Brown, Wixted, Baldo, & Delis, 2002). Finally, a chance-adjusted semantic clustering score consisting of the observed clustering score relative to the subject's chance-expected clustering score was calculated; this score served as the primary index of semantic clustering.

The recognition memory trial consists of the 9 target items and 18 distractors presented in a randomly ordered array; subjects were to respond "yes" if the item was from the target list and "no" if it was not. Level of performance on a yes–no recognition memory test is reflected in the number of correct hits and false-positive errors. These data yield two measures of recognition memory that have been adapted from signal detection theory: recognition discriminability and response bias. Discriminability refers to the ability to distinguish target words from distractor words, and it is widely considered to be the best measure of recognition memory accuracy. The discriminability index, or *d*', is analogous to a contrast *z* score reflecting the absolute difference in standard deviation units between the subjects hit rate and false-positive rate.

Performance on a recognition memory test is also influenced by response bias, which is the tendency to favor "yes" or "no" responses, particularly when there is uncertainty about the correct response. Response bias is theoretically independent of recognition discriminability (Donaldson, 1992), that is, subjects can exhibit a positive (i.e., "yes") or negative (i.e., "no") response bias when discriminability is high or low. The response bias measure used in this study is a parametric measure of *C* (for criterion level) that is defined as −0.5 (*z* score of hit

rate + *z* score of false-positive rate). More negative scores reflect a positive or "yes" response set, and more positive scores reflect a negative or "no" response set.

Neuroimaging

MRI data were obtained on a 1.5 Tesla Siemens Vision System (Siemens Inc., Iselin, NJ), using a standard quadrature head coil. A vacuum-molded head holder (Vac-Pac, Olympic Medical, Seattle, WA) was used to restrict head movements. Structural MRI data were acquired using a double spin echo sequence (DSE) with TR/TE1/TE2 = 2,500/20/80 ms timing, 1.00 × 1.25 mm^2 in-plane resolution, and about 50 contiguous 3-mm thick axial slices oriented along the optic nerve as seen from a midsection sagittal scout magnetic resonance image. In addition, a volumetric magnetization-prepared rapid gradient echo (MPRAGE) sequence was acquired, with TR/TE/TI = 10/7/300 ms timing, 15° flip angle, 1.00 × 1.00 mm^2 in-plane resolution, and 1.40-mm thick coronal partitions, and oriented orthogonal to the image planes of DSE. Proton density and T2-weighted images from DSE and T1-weighted images from MPRAGE were used together for tissue segmentation.

Subject brains were first segmented into gray matter, white matter, and cerebrospinal fluid using previously described methods (Tanabe et al., 1997). Briefly, the locally developed software uses simultaneously acquired proton density, T2-weighted, and T1-weighted magnetic resonance images to automatically classify tissues into the three major tissue types. Further separation of cortical from subcortical gray matter, ventricular cerebrospinal fluid (CSF) from sulcal CSF, and normal white matter from white matter lesions was performed manually by trained operators.

Volumes were obtained for the total cortical volume, frontal lobes, anterior temporal lobes, and posterior cortex in all subjects. Total cortical volume was the volume of all voxels designated as cortical gray matter after automated image segmentation and manual editing. To obtain frontal volumes, we circled the frontal lobes in the axial plane directly on the segmented images, using coregistered T1 weighted images as a guide. The central sulci and Sylvian fissures were used as landmarks for the posterior border, whereas CSF defined the lateral, medial, superior, and inferior surfaces. The central sulcus and Sylvian fissure are easily identified in the axial plane by their characteristic morphologies and position, including the fact that the central sulcus reliably extends to the interhemispheric fissure in the most superior slices in the axial plane. The only difficult point for identifying the frontal lobes is determining the slice on which the central sulcus has dissipated, and thus the Sylvian fissure should be used for delineation inferior to that slice. In our slice orientation, this was signaled by the appearance of insular cortex medial to the cortical mantle. Once insular cortex was identified, frontal lobe tracings used the Sylvian, rather than central sulcus, as the posterior margin of the frontal lobe. No attempt was made to define the posterior border of the frontal lobe medially using specific sulcal landmarks. Rather, a straight line was drawn between the medial ends of the central sulci or the anterior margins of the insula in each hemisphere to complete tracings. On slices below the corpus callosum, posterior margins were completed medially by extending tracings from the anterior margins of the insula posteriorly and medially to include all cortex anterior to the third ventricle at the level of the diencephalon, and anterior to the chiasmatic cistern at midbrain levels. The anterior temporal lobe was segmented on coronal T1-weighted images, beginning anteriorly with the first appearance of temporal tissue, and with the posterior border being defined as the entorhinal sulcus–uncinate fasciculus. Moving posteriorly, the uncinate fasciculus was designated as having appeared once there was a clear vertical connection between the frontal and temporal lobes. This point is sometimes referred to as the temporal stem (Colchester et al., 2001). This closure of the space between the frontal and temporal lobes also defines the entorhinal sulcus medially (Watson et al., 1992). All other borders were defined by CSF. A measure of posterior cortex was obtained by subtracting the frontal and anterior

temporal volumes from total cortical volume. This region included posterior temporal cortex, parietal lobes, and occipital cortex, and it was included in all of the regression analyses as a control for global cortical atrophy.

Intrarater reliability for the frontal and anterior temporal measures was established by having an experienced operator obtain frontal and anterior temporal volumes from 8 subjects (3 AD patients and 5 controls) twice, with ratings separated by at least 2 weeks (a total of 16 measures of each structure; Rosen, Gorno-Tempini, et al., 2002; Rosen, Kramer, et al., 2002). Intraclass correlation coefficients for the frontal and anterior temporal volumes were 0.99 and 0.97, respectively.

Semiautomated hippocampal voluming was carried out using a commercially available high dimensional brain mapping tool (Medtronic Surgical Navigation Technologies, Louisville, CO) that combined a coarse and then a fine transformation to match cerebral magnetic resonance images with a template brain (Csernansky et al., 1998, 2000). Measurement of hippocampal volume is achieved first by reslicing the MRIs along the main axis of the hippocampus and then manually placing 22 control points as local landmarks for the hippocampus on the individual brain MRIs: one landmark at the hippocampal head, one at the tail, and four per image (i.e., at the superior, inferior, medial, and lateral boundaries) on five equally spaced images perpendicular to the long axis of the hippocampus. Second, fluid image transformation was used to match the individual brains to a template brain, and pixels corresponding to hippocampus were labeled and counted to obtain volumes (Christensen, Joshi, & Miller, 1997). This method of semiautomated hippocampal voluming has well-documented reliability, with intraclass coefficients of .94, and correlations of greater than .91 with manual tracings, even in patients with considerable hippocampal atrophy (Hsu et al., 2002).

Regional volumes were corrected for differences in head size by normalizing the regional volume using the total intracranial volume, which is the sum of all tissue and fluid volumes measured inside the skull (obtained from the segmented image). This was accomplished by dividing each subject's total intracranial volume by 1,450, which is a typical total intracranial volume for a normal subject in our cohort, to obtain a normalization factor. Regions of interest were then multiplied by this normalization factor. Memory scores and MRI volumetric data are summarized in Table 2.

Statistical Analyses

The goal of this study was to determine which MRI variables best predict different aspects of episodic memory functioning. To accomplish this goal, we carried out four separate hierarchical regression analyses. In each analysis, the memory measure (delayed recall, semantic clustering, recognition discriminability, and response bias) was the dependent variable. Diagnosis was entered into the model in the first step to control for possible group differences on the dependent measure. In the second step, the four MRI measures (frontal, anterior temporal, posterior, and hippocampal volumes) were simultaneously entered as predictor variables. Follow-up regression analyses were carried out that included diagnosis by regional volume interaction terms to further rule out the possibility that results were being skewed by data from a single diagnostic group.

Results

Group differences were found for delayed free recall, recognition discriminability, and all four volumetric measures. Tukey's post hoc contrasts indicated that for delayed free recall, normal controls performed better than the three dementia groups (ps < .001) and the FTD group performed better than the AD group (p <.05). For recognition discriminability, normal controls performed better than the three dementia groups (ps <.01); the dementia subjects performed

comparably (*p*s > .80). Normal controls had larger frontal volumes than the dementia groups (*p*s < .05), and the AD and SD groups had larger frontal volumes than the FTD group (*p*s < .01). In contrast, the normal controls and AD and FTD groups had larger anterior temporal volumes than the SD group (*p*s < .05), with no differences between normal controls and AD ($p < .40$). There were no differences between the dementia groups on hippocampal or posterior volumes (*p*s > .25). Normal controls had the largest hippocampal volumes ($p = .07$ vs. AD and FTD; $p < .01$ vs. SD) and posterior volumes ($p < .01$ vs. AD and FTD; $p = .10$ vs. SD).

Results of the multiple regressions are summarized in Table 3, which shows the data for delayed free recall. Total number of words correctly recalled on the 10-min delayed recall trial (regressed over immediate recall) served as the index of memory accuracy during recall. When entered into the first step of the model, diagnosis did not explain a significant percentage of the variance. The overall model explained 18.7% of the variance. Hippocampal volume was the best predictor of delayed recall and was the only MRI variable that remained in the regression model and, when entered alone after diagnosis, explained an additional 12% of the variance. Semantic clustering during the four learning trials served as the index of strategic processing; these data are summarized in Table 3. The overall model explained 20.2% of the variance in semantic clustering. In contrast to delayed recall, frontal volume was the best predictor of semantic clustering and the only MRI variable that remained in the regression model. After controlling for diagnosis, frontal volumes explained an addition 20.1% of the variance.

A similar pattern of results emerged for the recognition memory scores, which are summarized in Table 3. Recognition discriminability was the measure of recognition memory accuracy. When the MRI variables were entered into the regression analysis after diagnosis, they explained an additional 21.6% of the variance. Hippocampal volumes were the best and only MRI predictor of discriminability. When entered alone into the regression model after diagnosis, hippocampal volume accounted for an additional 10.9% of the variance. For the model predicting response bias, the MRI variables independently predicted 16.2% of the variance. Frontal volume was the only MRI variable significantly predicting response bias, with smaller frontal volumes associated with a more liberal response bias. When entered separately into the regression model after diagnosis, frontal volume explained an additional 7.8% of the variance. Follow-up regression models were carried out that included diagnosis by region of interest interaction terms to address the possibility that the results were skewed by one of the diagnostic groups. None of the interaction terms remained in the model for any of the memory scores.

Discussion

The major findings of this study were that (a) hippocampal volumes and not other brain regions were associated with levels of memory accuracy in recall and recognition and (b) frontal volumes and not hippocampus or other cortical regions were associated with the use of strategic or decision-making aspects of recall and recognition.

Consistent with a large body of cognitive neuroscience literature, hippocampal volumes were the best predictor of memory accuracy after periods of delay. This finding occurred for both recall, as measured by a 10-min delayed free-recall trial, and recognition, as measured by an index of recognition discriminability on a 10-min delayed recognition memory trial. There were no independent contributions of posterior, anterior temporal, or frontal cortex to level of memory accuracy.

In contrast to its role in memory accuracy, hippocampal volume did not contribute to the variance in either of the strategic processing measures. Rather, semantic clustering and

response bias were best predicted by frontal volumes. The semantic clustering data are consistent with the view that the prefrontal cortex plays a critical role in organizing target material for more efficient encoding and retrieval of information in episodic memory (Becker & Lim, 2003). Less is known about response bias, but several studies have linked frontal lobe injury to an increase in a “yes” response bias (Alexander et al., 2003; Curran et al., 1997).

These results are consistent with our hypotheses and indicate a dissociation between frontal and hippocampal contributions to episodic memory performance. Support for a possible dissociation between frontal and hippocampal structures also comes from activation studies with normals. In one study, Bor, Duncan, Wiseman, and Owen (2003) used fMRI to evaluate the effect of using material that can be reorganized into higher level groups or chunks. Although structured sequences were easier to remember, increased activation of lateral frontal cortex was noted relative to unstructured sequences. A contribution of left prefrontal cortex to organizational processing during encoding has also been seen with studies using PET (Fletcher, Shallice, & Dolan, 1998).

One significant contribution of the present study was the inclusion of several brain regions in the prediction of memory performance. Atrophy in multiple brain regions can be found in normal aging and in neurodegenerative disorders, including relatively focal neurodegenerative conditions like FTD. The inclusion of multiple brain regions, particularly the relatively large posterior cortical area, in the regression models provided an important control for generalized atrophy and helped clarify the relatively unique contributions frontal and hippocampal regions have on difference aspects of memory performance.

Although we found an association between frontal volumes and semantic clustering, Glosser, Gallo, Clark, and Grossman (2002) compared FTD and AD on a list-learning paradigm and reported that the groups did not differ in their use of semantic clustering strategies during learning. The absence of group differences in their study is not incompatible with our findings, however. We also did not find group differences on semantic clustering. In addition, Glosser et al. used a different index of semantic clustering that may have been less sensitive. Finally, AD patients can have considerable frontal atrophy. In our sample, for example, although FTD subjects had smaller mean frontal volumes than AD subjects, the AD group had smaller frontal volumes than controls, and there was a fair amount of overlap in the distributions of frontal volumes in our AD and FTD groups. These data suggest that the relationship between frontal lobes and strategy use generalizes across diagnoses. In general, changes in cognition are probably driven more by the location and pattern of regional pathology than by the specific underlying disease state. AD pathology, for example, will present more like FTD than like typical AD when the plaques and tangles are predominately in the frontal lobe (Johnson, Head, Kim, Starr, & Cotman, 1999).

Models of memory emphasize networks, with the medial temporal lobe working in concert with the cerebral cortex (Eichenbaum, Schoenbaum, Young, & Bunsey, 1996; O’Reilly & Rudy, 2001). Although our results examined the relationships between the hippocampus and memory accuracy on the one hand, and frontal structures and strategy use on the other, our findings are compatible with these models. Several studies indicate that successful recollection of episodic information is associated with activation of lateral parietal cortex (Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998; Rugg, Otten, & Henson, 2002), and nonmnemestic abilities such as attention, categorization, search and retrieval strategies, expectation, and familiarity judgment contribute to memory performance. The frontal lobes also influence memory accuracy because of their involvement in encoding and retrieval (Fletcher, Shallice, & Dolan, 1998; Fletcher, Shallice, Frith, et al., 1998). Their role in organization during encoding has been highlighted by the current study and is supported by PET studies suggesting that left prefrontal cortex activation reflects organization processes (Fletcher & Henson,

2001). Application of clustering and other organizational strategies is known to facilitate recall performance (Delis, Freeland, Kramer, & Kaplan, 1988). The results of this study are consistent with network models insofar as they highlight the contributions of multiple brain regions to episodic memory performance.

One noteworthy finding was the small hippocampal volumes of our FTD and SD groups. This is consistent with reports from other investigators (Chan et al., 2001; Galton et al., 2001; Studholme et al., 2004). Studholme et al. (2004), for example, compared 20 subjects diagnosed with SD with 20 cognitively normal subjects using whole brain deformation tensor morphometry to study spatially consistent differences in local anatomical size. General linear modeling at each voxel was used to decompose the influence of age and head size from the primary diagnosis. Maps of the *T* statistic of the diagnosis across the 40 subjects highlighted significant ($p < .01$ Bonferroni corrected) focal tissue contraction effects related to dementia diagnosis in the left temporal pole extending into the hippocampus. Similarly, Galton et al. (2001) noted that hippocampal atrophy is not specific for AD but is also seen in SD. Significant hippocampal atrophy has also been reported in FTD (Broe et al., 2003; Kril & Halliday, 2004).

There were no group differences on our measure of semantic clustering, although relative impairments in use of semantic information might have been predicted for our SD subjects. A number of factors potentially contributed to this lack of relative impairment. Previous studies have found that SD patients can perform normally on tasks requiring access to superordinate information (Borgo, Mondini, & Bisiacchi, 2003). There were also several attributes of the CVLT-SF items that made them more accessible to SD patients. The task uses relatively high-frequency words from high-frequency categories, the object names are acquired fairly early in development, two of the categories were inanimate objects, and all of the list items are objects that are commonly manipulated; the combination of these factors makes the list items more accessible even for SD patients (Lambon Ralph, Graham, Ellis, & Hodges, 1998). Another contributing factor could be that our subjects were older, and even normal subjects show drops in semantic clustering with age.

Although one of the strengths of the CVLT-SF is that it simultaneously assesses multiple aspects of memory performance, assessing memory constructs with a clinical instrument is also one of this study's limitations. For example, the CVLT-SF has delayed recall trials that can potentially confound the results of the delayed recognition condition. The recognition task is also subject to criticism because of the ratio of studied and nonstudied values (Donaldson, 1992; Snodgrass & Corwin, 1988). The CVLT-SF recognition task includes twice as many distractors as target words. Although this was done to make the task more difficult and enables a comparison between semantically related and semantically unrelated distractors, the response bias measure calculated by the CVLT-SF may not reflect the true response bias of the subject. Replication of our findings using a recognition memory task that has more items and fewer learning trials (and therefore less risk of a ceiling effect), no delayed recall trials, and a recognition condition with equal numbers of targets and distractors is needed. A related concern is the potential lack of independence of our measures of semantic clustering and response bias. This is an important issue; although both variables were predicted by frontal volumes, the findings are weakened if they share too much variance. Fortunately, univariate analyses indicated reasonable independence of these measures ($r = .096$, $p = .34$). Another potential limitation to the study is our use of patients with neurodegenerative disease and diffuse cerebral atrophy. Although our statistical approach helped control for overall atrophy, studying patients with focal lesions avoids the potential confounds associated with more widespread cerebral involvement. Finally, our cognitive measures are complex and multifactorial. Semantic clustering, for example, requires awareness of the semantic attributes of the stimuli and thus can be impaired from organizational deficits or from semantic impairment. Similarly, although

our findings suggested specific brain–behavior relationships, other structural, functional, or even biochemical changes could very well have influenced our episodic memory measures.

Clinicians often associate poor memory performance with medial temporal pathology. One ramification of the current study is that episodic memory is a complex cognitive process dependent on the contributions of multiple brain regions, with accuracy of recall and recognition memory being more hippocampal mediated, whereas frontal regions make a more significant contribution to semantic clustering and response bias. One goal for future clinical research is a better understanding of the different ways in which memory can break down, which includes identifying the neuro-anatomical and other substrates of these memory components.

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Table 1

Demographics

Demographic	Normals (*n* = 8)		AD (*n* = 13)		FTD (*n* = 11)		SD (*n* = 10)	
	M	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***
Age	69.1	9.1	66.1	9.8	60.4	10.2	64.5	7.4
Education	15.5	3.5	16.5	3.5	15.1	1.6	17.4	3.5
MMSE score	29.5	0.5	22.3	4.8	21.9	6.0	22.7	4.6
Male:Female ratio	3:5		7:6		6:5		5:5	

Note. AD = Alzheimer's disease; FTD = frontotemporal dementia; SD = semantic dementia; MMSE = Mini-Mental State Examination.

Table 2

Memory Scores and MRI Volumes

	Control		AD		FTD		SD		
Memory measure	***M***	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***	***F*(3, 38)**
Recall (max. = 9)	7.00	1.1	0.54	1.2	2.64	2.1	2.00	2.5	21.5***
Semantic clustering	0.17	1.1	0.05	0.6	−0.34	0.3	0.20	0.7	1.1
Discriminability	3.29	0.3	1.35	0.6	1.69	1.3	1.59	1.1	8.0***
Response bias	0.11	0.2	−0.19	0.8	−0.30	0.8	0.25	0.6	1.4
Frontal lobes	195.28	14.4	175.17	14.3	150.07	18.5	175.48	14.0	13.7***
Hippocampus	4.74	0.9	3.77	0.8	3.73	0.9	3.10	0.8	5.5**
Anterior temporal lobes	29.01	4.6	25.43	5.2	22.45	6.0	13.86	4.1	15.3***
Posterior cortex	390.46	17.8	346.42	34.4	350.46	23.2	362.42	14.4	5.8**

Note. MRI volumes are in cubic centimeters. max. = maximum; AD = Alzheimer's disease; FTD = frontotemporal dementia; SD = semantic dementia.

** $p < .01$.

*** $p < .001$.

Table 3

Predictors of Delayed Recall, Semantic Clustering, Recognition Discriminability, and Response Bias

Predictor	*β*	*T*
	Delayed recall	
Hippocampus	.469	2.51*
Frontal lobes	−.248	−1.27
Anterior temporal lobes	−.188	−0.82
Posterior cortex	.094	0.51
	Semantic clustering	
Hippocampus	−.159	−0.84
Frontal lobes	.481	2.39*
Anterior temporal lobes	.035	−0.15
Posterior cortex	−.005	−0.30
	Recognition discriminability	
Hippocampus	.378	2.27*
Frontal lobes	.136	0.78
Anterior temporal lobes	−.104	−0.51
Posterior cortex	.248	1.50
	Response bias	
Hippocampus	−.002	0.06
Frontal lobes	.487	2.46*
Anterior temporal lobes	−.167	−0.72
Posterior cortex	−.310	−1.65

* $p = .05$.