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Mesial temporal, diencephalic, and striatal contributions to deficits in single word reading, word priming, and recognition memory

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Abstract

Fifty-three volunteer participants were studied with the fade-in task (Ostergaard, 1998) to measure naming latency, word priming, and recognition-memory performance, and with morphometric magnetic resonance imaging (MRI) techniques to measure volumes of mesial temporal lobe, diencephalic, striatal, and neocortical structures. The relationship between measures of cerebral volume loss and performance deficits was modeled using simultaneous regression analyses in which the behavioral measures were dependent variables. The results suggested that damage in both hippocampal and amygdala/entorhinal areas as well as damage in the diencephalon and the nucleus accumbens all contributed independently to the severity of recognition-memory deficits. Both caudate nucleus damage and hippocampal damage contributed independently to increased naming latency (slowed single-word reading). Finally, only damage in the hippocampus appeared to result in decreased word priming. These results provide further evidence against the assertion that word priming represents a form of memory unaffected by damage to the mesial temporal lobes. (*JINS*, 2001, *7*, 63–78.)

Keywords: Memory, Priming, Hippocampus, Caudate nucleus, Nucleus accumbens, Diencephalon, Magnetic resonance imaging

INTRODUCTION

The terms explicit and implicit memory were first used to describe distinctions between tasks that require conscious recollection of experience (explicit) and tasks in which performance is facilitated by previous experience but for which recollection of the previous experience is not required (Graf & Schacter, 1985). Priming refers to a striking implicit memory phenomenon wherein the mere perception of an item affects subsequent processing of that item. For example, identification of visually degraded or visually fragmented stimuli is facilitated by recent exposure to the stimuli. In several studies of amnesic patients and controls, the patients' performances on priming tasks appeared to be normal, despite the fact that they demonstrated severely compromised explicit (recall or recognition) memory for the same materials (Cermak et al., 1985; Gardner et al., 1973; Graf et al., 1984;

Jacoby & Witherspoon, 1982; Schacter & Church, 1995; Shimamura & Squire, 1984). This evidence, which has been reviewed extensively elsewhere (Ostergaard & Jernigan, 1993; Squire et al., 1993), has given rise to hypotheses that priming and explicit memory are mediated by separate memory systems with different neuroanatomical substrates (Gabrieli et al., 1990; Schacter, 1990; Squire, 1992; Tulving, 1985; Tulving & Schacter, 1990). Only the explicit memory system, it is argued, is impaired in amnesia. On the basis of this evidence, it has been hypothesized that the explicit memory system includes mesial temporal lobe and diencephalic structures that are damaged in amnesic patients, while priming is mediated by other (possibly neocortical) structures (Gabrieli et al., 1990; Schacter, 1992; Squire, 1992).

Patients with progressive dementias, notably patients with Alzheimer's disease (AD), have explicit memory deficits comparable to those of amnesic patients; however the results of some studies suggest that memory impairment in these patients may include priming deficits as well (cf. Keane et al., 1991; Ostergaard, 1994; Salmon et al., 1988). Since AD patients exhibit significant post-rolandic neocortical de-

generation, as well as mesial temporal lobe atrophy, it has been suggested that their priming deficits may reflect damage to a memory system located within temporal-parietal and/or occipital cortical regions (Gabrieli et al., 1990; Keane et al., 1991; Polster et al., 1991; Schacter, 1991).

However, several findings are in conflict with these conclusions. Reports of normal or near-normal priming in AD patients on some tasks indicate that their priming performance may not invariably be compromised (Keane et al., 1991; Ober & Shenaut, 1988). Furthermore, findings of impaired priming in amnesia are far more common than generally acknowledged. Even in the original studies by Warrington and Weiskrantz (1968) and Milner et al. (1968), there was evidence of impaired priming in amnesic patients; and subsequently, impaired priming in amnesia has been reported with many different priming tasks (Cermak et al., 1985; Cohen & Squire, 1980; Gabrieli et al., 1984; Ostergaard, 1994, 1999; Rich et al., 1996; Schacter et al., 1995; Smith & Oscar-Berman, 1990; Squire et al., 1987; Verfaellie et al., 1991).

Similar issues arise in studies of the memory decline of normal aging. Elderly subjects evidence a clear decline in explicit memory (for a review see, Light, 1991). On the other hand, several investigators have detected no age effects on priming measures (Light & Singh, 1987; Light et al., 1986; Schacter et al., 1992). It has been suggested that this pattern of memory change bears a qualitative resemblance to the pattern of deficits seen in amnesic patients (Light & Singh, 1987). However, other investigators have found a significant decline in priming in older compared to young individuals (Chiarello & Hoyer, 1988; Davis et al., 1990; Hultsch et al., 1991). Such findings have lead to comparisons between memory impairments in normal aging and in AD, and it has been suggested that AD may represent a more severe, or accelerated, form of normal age-related memory decline associated with degeneration in the mesial temporal lobe system.

Several investigators have attempted to determine the neural bases of priming and explicit memory functions. As noted above, initially inferences were drawn based on the well-documented association of explicit memory impairment with damage in mesial temporal lobe and diencephalic regions. Since patients with amnesia, and known damage to these regions, appeared to have preserved priming, it was assumed that these structures do not mediate priming effects. On the other hand, patients with cortical dementia (AD) did exhibit priming deficits; therefore, some hypothesized that intrinsic cortical mechanisms might mediate priming effects. Previous research has suggested that occipital lobe damage impairs visual perceptual priming, and can leave recognition memory for the visual material intact (Gabrieli et al., 1995). This is surprising, given that the visual representations that are presumably retrieved for recognition memory are themselves thought to reside in occipital cortex. Nevertheless, this work would appear to provide strong evidence for dependence of perceptual priming on occipital lobe structures. A more recent study of the effects of mesial

temporal lobe damage suggested that while skill learning was intact in patients with such damage, implicit memory for visual context was impaired (Chun & Phelps, 1999). These authors concluded that the mesial temporal lobe structures do play a role in implicit (or nonconscious) memory when the task requires the binding of multiple cues.

In recent years, neural bases of memory functions have increasingly been investigated with functional imaging. These studies have sometimes produced surprising results. For example, many studies contrasting explicit memory with baseline conditions have produced no evidence of mesial temporal lobe activation by explicit memory tasks *per se* (Haxby et al., 1993; Jernigan et al., 1998; Kapur et al., 1995b; Moscovitch et al., 1995; Shallice et al., 1994; Tulving et al., 1994b). However mesial temporal lobe activation has been observed in association with cued recall (Buckner et al., 1995; Schacter et al., 1996; Squire et al., 1992). In addition, several investigators have demonstrated mesial temporal lobe activation under novel picture and novel word-encoding conditions (Grady et al., 1995; Kapur et al., 1995a; Martin et al., 1997; Stern et al., 1996); however, the results of some studies suggest that mesial temporal lobe activation may result from task demands for semantic association (Henke et al., 1999); and may not require stimulus novelty (Brewer et al., 1998; Wagner et al., 1998).

Predominantly right hemisphere prefrontal activations are consistently observed in studies involving retrieval of recently studied material, regardless of the nature (verbal or figural) of that material, and regardless of whether the task requires recognition or recall (Jernigan et al., 1998; Nyberg et al., 1996; Tulving et al., 1994a). These observations led Tulving and associates to postulate that a system in the right hemisphere is specialized for retrieval from episodic memory, while a left hemisphere system mediates encoding and retrieval from semantic memory. Recent studies suggest that the encoding/retrieval distinction interacts with the nature of the stimulus material used in determining the laterality of activations (see Desgranges et al., 1998 for review). The findings of one recent study of activation by semantic and episodic memory retrieval (Wiggs et al., 1999) were, in some respects, inconsistent with the predictions of the HERA model, in that semantic retrieval invoked as much or more activation in right frontal areas than did episodic retrieval.

In studies with implicit memory conditions, reduced activity in occipital cortical sites associated with the processing of studied relative to novel material has been reported repeatedly (Buckner et al., 1995; Schacter et al., 1996; Squire et al., 1992; Tulving et al., 1994b), and some have speculated that this deactivation is the neural substrate of priming. In one recent study, conducted specifically to examine activation during implicit memory, Beauregard et al. (1998) found right hippocampal activation by a primed semantic-classification task relative to an unprimed task. The "brief multiple presentation" method was used to prime the items in an attempt to preclude conscious recollection. The results were interpreted by the authors to show a role for mesial temporal lobe function in implicit memory. One difficulty

with the interpretation, however, is that the primed task always preceded the unprimed task, so the result could have been related to decreased task novelty. This is an important consideration, since Martin et al. (1997) reported that right mesial temporal lobe activation associated with processing novel words and nonwords was diminished when the task was repeated, even with a new set of novel stimuli. The findings of the Beauregard et al. study differed from those of another study using subliminal presentation of stimuli (Elliott & Dolan, 1998), in which repeated items evoked significantly less mesial temporal lobe activation than novel items. In summary, functional imaging studies of memory, particularly those employing visually presented stimulus material, implicate frontal and occipital regions in addition to mesial temporal lobe structures, though the role that these structures play in implicit and explicit memory processes remains unclear.

In a previous anatomical study using sMRI (Jernigan & Ostergaard, 1993), we examined the effects of damage (volume loss) in different brain structures on measures of priming and recognition memory in a group of participants who varied widely in their memory abilities. Priming effects were measured with a perceptual-identification task. It was in this study that we first observed that memory-disordered participants sometimes produced impaired performances on the baseline tasks from priming paradigms, and that damage in striatal structures appeared to contribute to this impairment. We also noted that impaired baseline performance (i.e., perceptual identification) was associated with higher priming scores, and that when the effect of baseline impairment was controlled, priming deficits were associated with mesial temporal lobe damage. These results suggested to us that the kind of memory measured as priming does not arise from neural mechanisms distinct from those of the mesial temporal lobes; and that, in fact, study effects on priming tasks may depend directly on the integrity of mesial temporal lobe function.

Since this study (Jernigan & Ostergaard, 1993) was completed, Ostergaard (1998) has developed a new theoretical approach for conceptualizing performance on priming tasks, aimed at explaining the discrepant findings obtained in priming studies. The information availability (IA) model accounts for priming effects in terms of the information available to the participants to carry out the priming task. In many priming tasks, participants are required to identify, name, or classify stimuli that are either presented in a complete form (e.g., words), presented very briefly in a tachistoscope, or presented in some incomplete form (e.g., visually degraded words or word stems). In the IA model, it is assumed that the participant will use any relevant information available from any source to carry out such tasks. In visual-identification tasks, the information available to the participants may be regarded as coming from three sources: perceptual information that is directly available from the stimulus (P); the information that is available in memory from a specific priming or study episode (S), and the information that is available from all other prior encounters with

the item (O). The information from a prior study or priming episode is, of course, only available for previously studied items, and not for items used to determine baseline performance level. For familiar items presented clearly, large amounts of P and O may be available relative to the S available from a prior study episode; and, therefore, the prior study episode may have only a small impact on overall performance (the priming effect will be small). An important prediction of the model is that often when familiar and/or perceptually clear items are used in priming tasks, only very small priming effects occur, and variability in priming effects is minimal, *regardless of how much information is available in memory from a prior study episode and regardless of how much subjects vary in this respect*. Unfamiliar or perceptually degraded items, on the other hand, will produce larger priming effects that reflect variability in the availability of study information to a larger extent.

Another prediction of the model is that, given that the amount of study information is kept constant, the factors that affect priming also affect baseline performance, and a strong relationship between baseline performance level and measured priming effects will occur. It should be possible to increase measured priming effects in a task by using unfamiliar rather than familiar items, or by degrading the stimuli such that less perceptual information is available. Poorer baseline performance should be associated with increased magnitude of priming. This relationship between baseline performance and priming is important when memory-impaired patients are compared to normal controls. If the patients have deficits that affect their baseline performance, this has to be taken into account when evaluating the priming effects (see Hamann et al., 1995; Jernigan & Ostergaard, 1993; Ostergaard, 1994; Ostergaard & Jernigan, 1993, 1996).

The fade-in task was developed by Ostergaard to test the predictions of the IA model by controlling baseline performance in word identification. In the task, items presented on a computer screen come gradually into view (fade in). The task is similar to the "perceptual clarification" procedures used by Johnston et al. (1985) and Perruchet and Baveux (1989). Words can appear instantly, or they can fade-in on the computer screen over a period of up to 5 s (see Ostergaard, 1998, for details of the method). Baseline word-naming speed is manipulated by varying the rate at which words are revealed. Priming is measured in this task by repeating words and comparing naming latency for the first and second occurrence of a word (priming is reflected in faster naming times for the second compared to the first occurrence). According to the IA model, the more slowly the items are clarified, the less visual-perceptual stimulus information is available to the participants at any given time, and, therefore, the more the participant will rely on information available in memory for identifying the words. Consequently, slower fade-in times should produce slower baseline identification latencies (task difficulty is increased), and larger priming effects that are more sensitive to experimental manipulations.

The predictions of the IA model have been tested and confirmed in a series of studies with normal individuals. Ostergaard (1998) demonstrated that as fade-in times were increased in a word-naming task, baseline naming latencies increased, and importantly, the magnitude of priming effects increased. Furthermore, manipulations of word frequency, length of delay between study and test, and number of repetitions of the studied items only affected priming in the slow fade-in conditions. No effects of these variables were observed when words were presented instantly or very rapidly (Ostergaard, 1998).

In a recent study, the priming performances of amnesics were examined using the fade-in task (Ostergaard, 1999). As in the previous fade-in experiments, baseline naming was slower and priming effects were larger in the slow than in the fast fade-in conditions. The most important finding was that in the slow fade-in condition, the amnesic patients evidenced significantly reduced priming compared to control participants. Furthermore, in a second experiment, in which the number of study repetitions was manipulated, the amnesic patients evidenced impaired simple (i.e., from the first to the second occurrence) priming, and they evidenced an additional impairment in that, unlike in the controls, their priming effects were not enhanced by further repetitions of the items.

These findings suggest that the memory which is measured as priming is not intact in patients with clinical memory impairment; rather that the apparent dissociation between priming and explicit memory performances is due to strong effects on priming measures of such factors as the amount of task-relevant perceptual or lexical information that is available to participants. Memory-impaired patients often appear to have "normal" priming because the priming effects in the control participants are constrained by their superior perceptual and lexical skills.

The principal goal of this study was to replicate and extend the findings in Jernigan and Ostergaard (1993) using the more sensitive priming measures obtained with the fade-in task, and improved anatomical methods, in order to better define the neural bases of deficits in priming and recognition memory. The present study employs morphometric techniques that provide improved sensitivity and anatomical specificity over those used in the previous anatomical study. For example, the present methods permit separate measurement of two functionally distinct parts of the striatum, the caudate nucleus and the more ventrally lying nucleus accumbens, as well as separate structures within the mesial temporal lobe. Furthermore, lobar divisions of the cerebral cortex were made based on the principal sulci, yielding improved measures of frontal and occipital lobe cortices. Based on the behavioral and anatomical results reviewed above, and the results of recent functional imaging studies, we have focused on the roles of specific structures consistently implicated in studies of memory, namely two mesial temporal lobe structures (the hippocampus and the amygdala/entorhinal region), the diencephalon, two striatal structures (caudate nucleus and nucleus accumbens), and frontal and occipital neocortex.

METHODS

Research Participants

As in our previous study, we have attempted to model the anatomical effects on the task measures in a mixed group of participants within which there is adequate range on all of the behavioral and anatomical factors. Many of the 53 participants (21 women and 33 men) included in the study had memory deficits, and the severity of these deficits varied from mild to severe. The clinically normal participants ($n = 34$) ranged in age from 24 to 99 years, but were predominantly elderly. They were screened for medical, psychiatric, or neurological disorders within one of several UCSD clinical research centers recruiting controls for neuropsychiatric studies. In addition, there were eight amnesics, aged 30–75 years; seven AD patients, aged 73–80 years; and four HD patients, aged 34–62 years. The amnesic, AD, and HD patients were also diagnosed by physician investigators within clinical research centers. A number of the elderly participants were genetically at-risk for AD by virtue of family history, or presence of an APO-E e4 allele. Thus the sources of brain volume loss included aging, and cerebral damage associated with alcoholism, thiamine deficiency, anoxia, AD, HD, and possible factors mediated by the e4+ genotype.

Fade-in Task

Design and materials

The word-naming task involved two within-subjects presentation conditions, a fast fade-in and a slow fade-in condition. The fade-in procedure has been described in detail elsewhere (Ostergaard, 1998, 1999). With this method, items presented on a computer screen come gradually into view and appear to fade in continuously and smoothly. In the fast fade-in condition each item was presented gradually over a period of 1 s, while in the slow fade-in condition items faded in over a 2.5-s period. The critical words were repeated and the final within-subjects factor in the naming task was occurrence, first or second.

Two matched blocks of word-naming trials were constructed, each consisting of 60 target words and 30 filler words. In each block, the mean frequency of the target words was 57.1 (range 1–255), and the mean length was seven letters (range 5–9). Within each block the 60 target words occurred twice, and the order of the resulting 120 critical trials within a block was randomized with the following restrictions: the lag between the two occurrences of target items was random within the range of 15–20 items, and repeated words occurred on no more than four successive trials. Twenty-five of the filler words were interspersed among the critical trials to satisfy these criteria. Additionally, the first five trials in each block were regarded as practice trials and the words used in these trials were filler words. In short, in each block of 150 trials, 60 target words were presented twice with lags varying from 15 to 20 items. One block was used

in the slow fade-in condition and the other block in the fast fade-in condition. The two blocks were rotated between fade-in conditions across participants.

Half of the participants were given the fast before the slow fade-in condition, and half of the participants were given the slow fade-in condition first.

A recognition-memory test was administered after each block of word-naming trials. In this test, the 60 target items from the immediately preceding block of naming trials were presented randomly mixed with 60 matched distractor (new) items.

Procedure

Stimulus presentation and recording of response latencies were controlled by an Apple IIGS microcomputer. The participant was seated at a comfortable viewing distance in front of the computer and was instructed that a long series of words would be presented on the computer screen, each preceded by a warning signal consisting of three plus signs (+++). The participant was told to read aloud (name) each word as quickly as possible, but without making errors. The participant was informed that the words would appear gradually on the computer screen and that many words would be repeated. The participant was then shown examples of words fading-in (appearing gradually).

Response latencies were measured with a voice-activated relay connected to the computer. On each trial, immediately following the first naming response to a word, the complete word was presented and remained on the screen for 3 s before the next trial was initiated. Immediately after the completion of the block of word-naming trials, the recognition-memory test was given. In this test, the 60 critical items from the preceding word-naming task together with 60 matched new items were presented, one at a time, in the same random order to all participants. In the recognition-memory task, the words were presented instantaneously on the screen (i.e., the words did not fade-in gradually). The participant was instructed that half of the words would have been read on the immediately preceding word-naming task and half would be new words. For each item, the participants decided if the word was an "old" or a "new" word. The participant was given a short rest period (approximately 10 min) between the two fade-in conditions.

Imaging Protocol

Three whole-brain image series were collected for each participant. The first was a gradient-echo (SPGR) T1-weighted series with TR = 24 ms, TE = 5 ms, NEX = 2, flip angle = 45 deg, field of view of 24 cm, section thickness of 1.2 mm, and no gaps. The second and third series were fast spin-echo (FSE) acquisitions yielding two separate image sets: TR = 3000 ms, TE = 17 ms, ET = 4 and TR = 3800 ms, TE = 102 ms, and ET = 8. For all series, the field of view was 24 cm. Section thickness for the FSE series was 4 mm, no gaps (interleaved).

Image Analysis

The image-analytic approach is similar to that used in our previous anatomical studies (Jernigan et al., 1990, 1991; Jernigan & Ostergaard, 1993), but represents a significant elaboration of these methods as described below. Trained anatomists who were blind to subject diagnosis, age, gender, or any other identifying information subjected each image data set to the following image analysis procedures:

1. Interactive isolation of intracranial regions from surrounding extracranial tissue.

2. Three-dimensional digital filtering of the matrix of pixel values representing brain voxels to reduce inhomogeneity artifact.

3. Reslicing of the volume to a standard orientation.

4. Tissue segmentation using semiautomated algorithms.

5. Neuroanatomical region-of-interest (R01) analysis.

Brain was first isolated from extracranial areas in the image, that is, from surrounding tissue that was in some instances contiguous with brain tissue and similar in signal value. This process results in a new volume within which the positions of brain voxels are coded, that is, a mask. The reproducibility of the stripping method was assessed by performing the stripping operations independently on six pairs of image volumes and comparing the within-pair discrepancies. Each pair represented two FSE volumes obtained on different occasions in the same individual. Discrepancies in brain volume were small (mean, .54%), ranging from .03% to 1.25% .

Filtering is applied to reduce nonbiological signal drift across the field of view, which is presumably due to field inhomogeneity and susceptibility effects. A three-dimensional (3D), high-pass filter is applied, with two iterations, separately to the "stripped" proton density weighted and T2-weighted FSE image volumes. First, a roughly cubic near-neighbor averaging filter is applied to produce a smoothed data set; then the original volume is divided by the smoothed data set on a voxel-by-voxel basis; and finally each voxel value is multiplied by the mean voxel value of the original data set. The dimensions of the cubic smoothing filter were chosen by subjective evaluation of the results obtained with a series of filter sizes and were set at approximately 30 mm. That is, the set of voxels averaged to create each voxel value in the smoothed data set spans 33 voxels in the x and y directions, and seven voxels in the z direction (i.e., it measures 31 mm $\times$ 31 mm $\times$ 28 mm). In constructing the smoothed data sets, near-neighbor averages are produced only for positions within the volumes coded as brain. Similarly, only the values for near-neighbors that are also brain voxels are averaged. This method is a 3D elaboration of the two-dimensional (2D) filtering method used in our previous anatomical studies.

The tissue-classification procedure is an interactive, supervised process. Operators manually designate the posi-

tions of three sets of tissue samples, one for each of the target tissues (gray, white, and cerebro-spinal fluid [CSF]). The goals are to obtain samples in standard anatomical locations within regions of homogeneous tissue, and to avoid artifacts and tissue abnormalities (such as ischemic damage). Samples are selected in locations that appear to be homogeneous and free of signal abnormalities both in the section to be sampled and in the adjacent sections. In most cases, the operators select samples in six gray matter locations (bilaterally in the caudate nucleus, putamen, and the pulvinar of the thalamus); in four white matter locations (bilaterally in the suprasylvian white matter at the level of the pulvinar, and in similar locations at the level of the caudate/putamen); and in four locations within CSF-filled structures (two samples are taken within the frontal horns, and two more posterior samples are taken at approximately the level of the trigones of the cerebral ventricles). The sample voxel values are then analyzed using simple regression techniques to separate first all brain parenchymal voxels from CSF voxels, and then gray matter voxels from white matter voxels. The regression coefficients obtained in these simple analyses are then applied to classify each voxel within the volume as most similar to CSF, gray matter, or white matter. Interoperator reliability of total tissue volumes for independent tissue classification by two anatomists was estimated using 11 brain data sets, and was .92 for white matter, .95 for gray matter, and .99 for CSF.

In order to facilitate anatomical region definition, resectioned data sets were aligned to a standardized stereotactic space defined relative to the decussations of the anterior and posterior commissures and the structural midline. This improved the reliability of boundary determination, facilitated reference to standard brain atlases, and made it possible to identify small structures more consistently. Registration of the T1-weighted and spin-echo data sets was accomplished so that registered sections from all three data sets were available to the operators when attempting to resolve anatomical boundaries. Anatomists circumscribed regions on tissue-segmented images. Standardized rules were applied for delineating a set of subcortical structures and cortical regions. Subcortical structures included the cerebral ventricles, the caudate nucleus, the nucleus accumbens, the lenticular nucleus, the thalamus, the substantia nigra, and a region referred to as basomesial diencephalon (which includes septal nuclei, mamillary bodies and other hypothalamic structures, the bed nucleus of the stria terminalis, and the diagonal band of Broca). Cortical regions included the temporal lobe, frontal lobe, parietal lobe, occipital lobe, cingulate cortex, and insular cortex. Separate measures were obtained of three mesial temporal lobe structures: the hippocampus, the amygdala and adjacent entorhinal cortex, and parahippocampal gyrus. The four major cortical lobes were drawn to include cortical gray matter, underlying white matter, and CSF. Each tissue was volumed separately within each lobe, and white matter and CSF were also measured in a deep subcortical zone not within any of the cortical lobes. Gray matter and adjacent CSF of the cingulate cortex and insular

cortex were defined separately. Representative fully processed images from a normal brain, illustrating the regional boundaries of many of the measured brain structures, are shown in Figure 1. ROI analysis of ten brain data sets was performed independently by two anatomists. Interoperator reliability for estimated volumes of the 15 primary gray matter structures ranged from .88 to .99, with reliability for most measures exceeding .95.

For the present study, the specific measures examined were volume estimates for seven gray matter regions: the hippocampus, the amygdala/entorhinal region, the diencephalon (defined as the summed volumes of the thalamus and the basomesial diencephalon), the caudate nucleus, the nucleus accumbens, the cortical gray matter of the frontal lobe, and the cortical gray matter of the occipital lobe.

The boundaries of the mesial temporal lobe structures, arguably of particular importance in the present study, are defined as follows (and illustrated in Figure 1): The mesial temporal lobe subregions include the amygdala/entorhinal area, the parahippocampal region (not included in the present analysis), and the hippocampal region. The hippocampal and parahippocampal regions extend posterior to the pulvinar of the thalamus where they lie inferior to the corpus callosum. These two regions extend anteriorly to (but not including) the section immediately posterior to the section in which the long columns of the fornix appear; that is, the anterior boundary is defined in part stereotactically. The transition to the amygdala/entorhinal region occurs in this (immediately posterior) section behind the long columns of the fornix and the region extends anteriorly to and includes the section at which the temporal pole is entirely separated from the frontal lobe by the lateral sulcus. Within the posterior zone, the parahippocampal region includes entorhinal, parahippocampal, and some lingual gyrus. The inferior boundary is the collateral sulcus and the superior boundary is defined by following the white matter through the bend in the parasubicular region, separating the subiculum (hippocampal region) from the entorhinal cortex. The more superior hippocampal region is primarily the hippocampal formation and retrosplenial gyri. In posterior sections where the temporal horns of the cerebral ventricles are seen, the hippocampal region includes the tail of the hippocampus, the fasciola cinerea, and the gyrus fasciolaris. The amygdala/entorhinal region includes amygdala, some very anterior hippocampus, contiguous entorhinal cortex, and the uncus (which includes perirhinal cortex).

Data Analysis

We first examined the behavioral measures obtained with the two fade-in conditions, namely baseline naming latency, priming, and recognition memory. We next examined the relationship between damage to the different brain regions and the observed deficits on the behavioral measures in separate multiple regression analyses for each behavioral measure. The role of occipital (but not frontal) neocortex damage in naming latency and priming was ex-
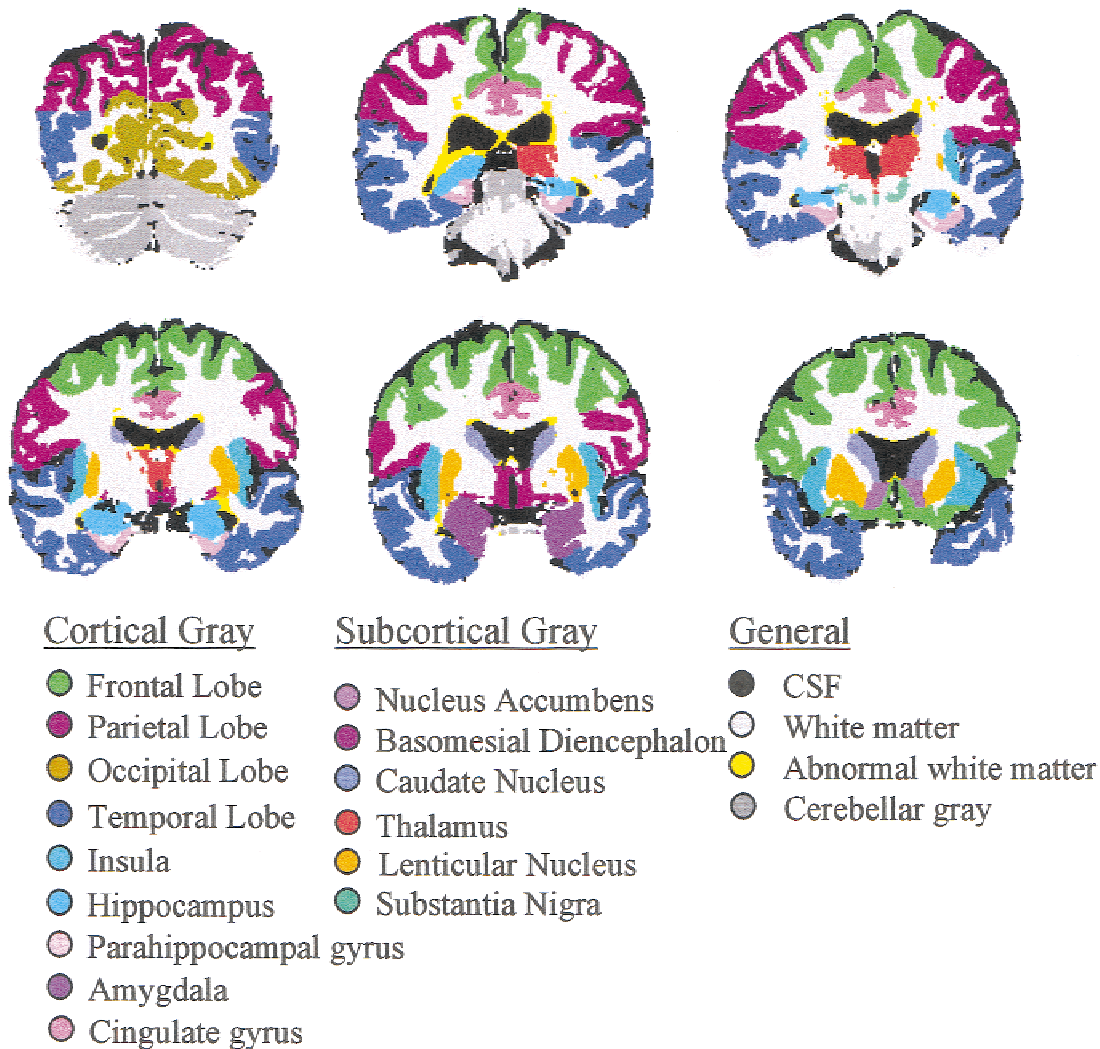
Fig. 1. Representative, fully processed images with gray matter voxels color coded to illustrate the placement of structural boundaries.

amined because the perceptual processing of the word forms we presented as stimuli is presumably carried out in this region, and because this is the putative neural substrate for repetition priming effects with visual word forms. The role of frontal (but not occipital) neocortex damage in recognition memory was examined because prefrontal structures have consistently been implicated in functional imaging studies of explicit memory. All subcortical measures were included in each regression analysis. The total supratentorial (cerebral) cranial volume was also included, as a covariate, in each regression analysis, to control for individual differences in head size. Thus, in each of the primary analyses the independent contributions of damage to six regions were estimated in simultaneous regression models (i.e., the six anatomical measures were regressed on each behavioral measure). The statistics of interest were the specific regression coefficients for the six anatomical measures.

RESULTS

Behavioral Results

The naming latency (i.e., latency on the first, or baseline, occurrence of the words), priming, and recognition memory results are summarized in Table 1. As expected, the fade-in manipulation resulted in highly significant increases in naming latency and priming, but had no effect on recognition memory (i.e., recognition memory for words that appeared quickly was no different than for words that faded-in slowly). Also, there was a dramatic reduction in the association between baseline naming latency and priming in the slow fade-in condition ($r = .00$, $p > .99$) relative to that in the fast fade-in condition ($r = .26$, $p < .07$), suggesting that the former represents a measure of priming that is less strongly constrained by high performance on the baseline

Table 1. Summary of behavioral results

	Naming latency (in ms)		Priming (in ms)		Recognition (% correct)	
	Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Fast	1304	(277)	105	(56)	.77	(.14)
Slow	2240	(461)	233	(106)	.78	(.15)
	$t = 27, p < .0001$		$t = 10, p < .0001$		$t = .43, p > .60$	

task, and thus is a more faithful measure of priming *per se*. Furthermore, priming in the slow fade-in condition was significantly correlated with recognition memory scores ($r = .46, p < .001$), while priming in the fast fade-in condition was not ($r = .14, p > .30$). Anatomical modeling was therefore performed on the baseline naming latency and priming measures from the slow fade-in condition, referred to henceforth as naming latency and priming, respectively. Since the fade-in manipulation had no effect on recognition memory,

the total percent correct on the combined recognition-memory tasks was computed. Henceforth the term "recognition memory" refers to this measure.

The primary behavioral measures (naming latency, priming, and recognition memory) are plotted against age in the panels of Figure 2. The diagnoses are indicated by symbol. The data are presented graphically in this way to reveal the extent to which the behavioral variability observed in the sample reflects age and disease factors. As is appar-
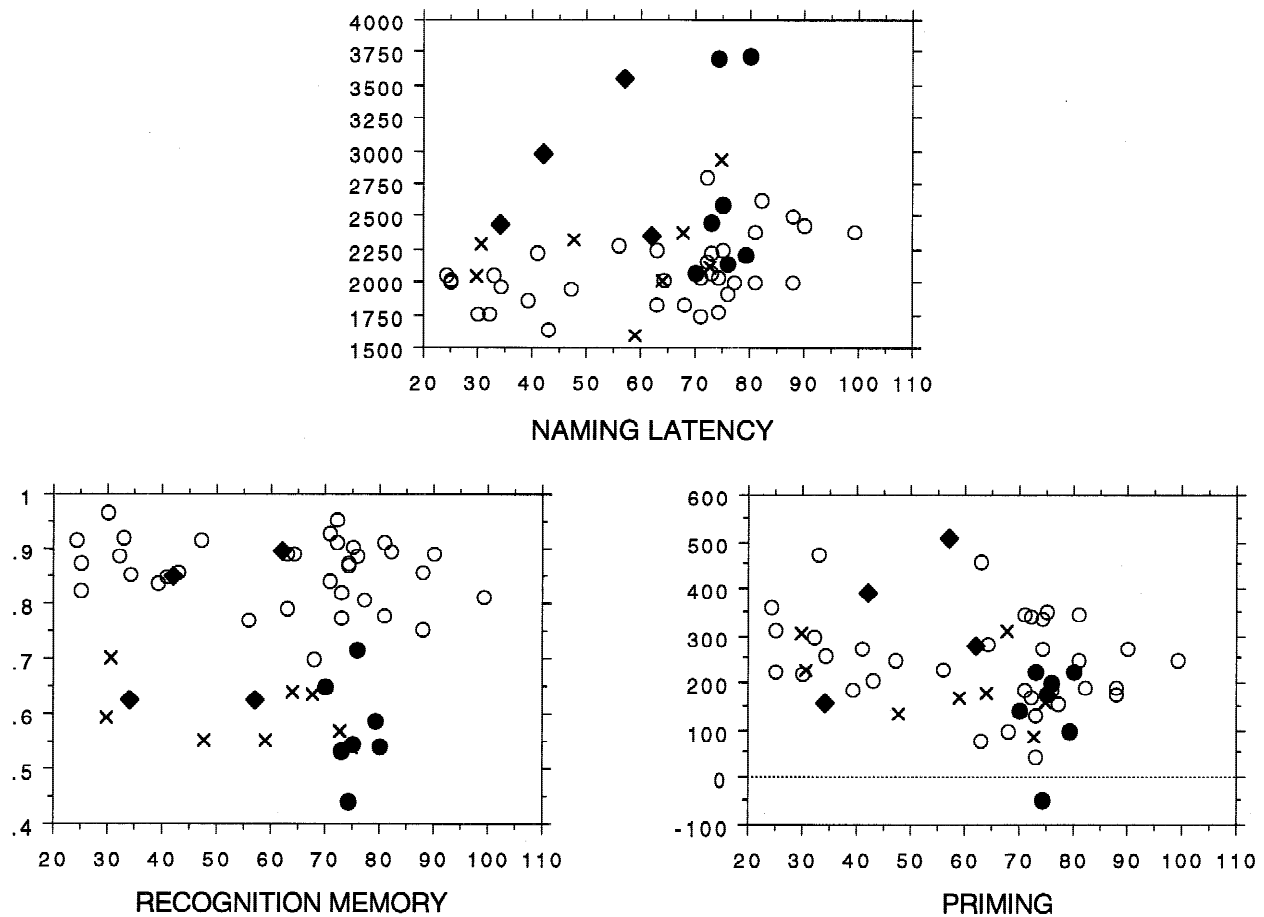

Fig. 2. Plots of the major behavioral variables (on the *y*-axes) against the age of the participants (on the *x*-axes). Naming latency and priming scores are both from the slow fade-in condition and are expressed in milliseconds. The recognition memory score is the total percent correct for both recognition memory tasks. The clinically normal participants' scores are plotted as open circles, the AD patients' scores as filled circles, the HD patients' scores as filled diamonds, and the amnesic patients' scores as **x**'s.

ent, the combined effects of these factors resulted in very substantial increases in variability over that observed within young normal participants. The resulting distributions of scores exhibit relatively continuous variation from excellent to severely impaired performance.

Anatomical Regression Results

Four of the anatomical measures are plotted against age in the panels of Figure 3. As described below, two of the measures, volumes of the hippocampus and the nucleus accumbens, contributed significantly in the anatomical models, while the other two, frontal and occipital cortical volumes, did not. Again, the combined effects of age and disease factors clearly result in increased variability over that observed within young normal participants; and, again, the values obtained range continuously from that characteristic of young adults to values suggestive of highly significant volume loss.

Results of the anatomical regression analyses are given in Table 2. The overall regression results for the recognition memory measure were significant ($F = 5.2, p < .001$). They provide further evidence for the strong relationship between mesial temporal lobe damage and recognition memory deficits, and they suggest that both hippocampal damage and damage to the more anterior mesial temporal region (including amygdala, entorhinal cortex, and perirhinal cortex) contributed independently. Within this sample of 53 individuals, it was possible to detect additional, independent, effects of diencephalic damage and damage to the nucleus accumbens that were not observed in Jernigan and Ostergaard (1993) with only 30 participants. Surprisingly, there was still no evidence that frontal lobe damage contributed to recognition-memory deficits. As shown in Figure 3, there is substantial variability in frontal lobe volume within the sample, though most appears to be due to age-related volume loss in older participants.

The overall regression for naming latency was also significant ($F = 5.38, p < .001$). As in our previous study, there was a significant association of striatal (particularly caudate) damage with increased naming latency. In addition there was evidence for an effect of hippocampal damage;
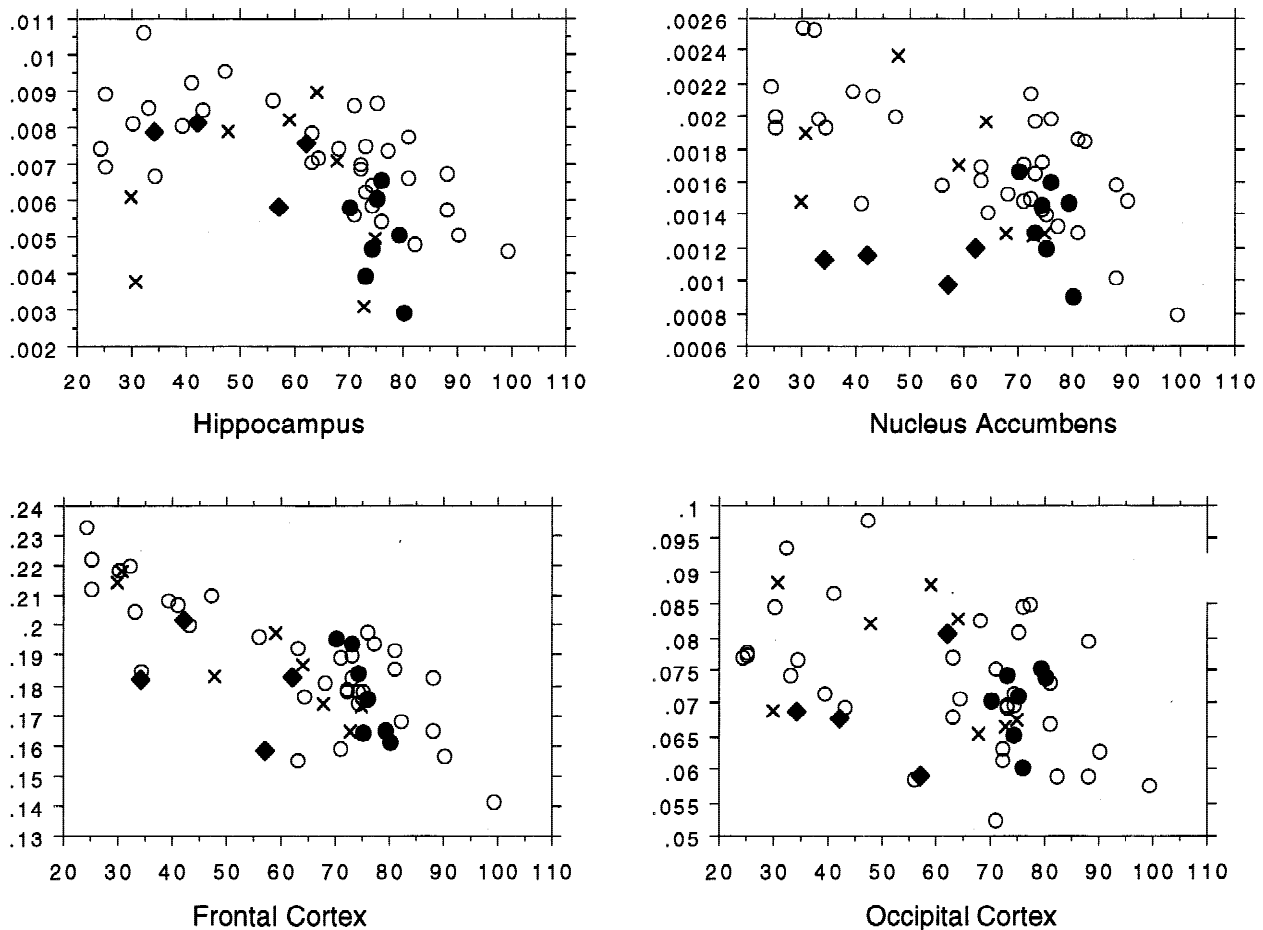

Fig. 3. Plots of four of the major anatomical measures (on the *y*-axes) against the age of the subjects (on the *x*-axes). In each case, the anatomical measure is the estimated volume expressed as a proportion of the volume of the participants' total supratentorial cranial vault. The clinically normal participants' values are plotted as open circles, the AD patients' values as filled circles, the HD patients' values as filled diamonds, and the amnesic patients' values as **x**'s.

Table 2. Results of regressions of anatomical variables on fade-in measures

	Recognition memory		Naming latency		Priming	
	β	p	β	p	β	p
Hippocampus	**.32**	**.03**	−.26	.07	**.36**	**.05**
Amygdala	**.25**	**.04**	−.13	.27	.08	.62
Diencephalon	**.39**	**.02**	−.03	.85	.12	.49
N. Accumbens	**.4**	**.04**	−.23	.18	−.12	.56
Caudate N.	−.02	.88	**−.32**	**.03**	−.17	.34
Occipital Cortex	—	—	−.18	.23	−.06	.74
Frontal Cortex	−.39	.17	—	—	—	—

the contribution of this variable approached significance. In fact, with a reduced model including only hippocampal and caudate volumes as predictors, both variables made highly significant contributions (β for hippocampus = −.45, $p <$ .001; β for caudate = −.43, $p < .01$). There were no significant contributions of diencephalic or occipital lobe damage.

The overall regression model for the priming measure did not approach significance, nor did most of the individual regression coefficients. However, the simple correlation between priming and the hippocampal measure (controlling for cranial volume) was significant ($r = .30$, $p < .05$); and in the complete model the regression coefficient for the hippocampal measure was also significant.

Post-hoc analyses of priming

As described above, the fade-in manipulation results in a substantial decrease in the proportion of variability in the priming measure that is attributable to variability in naming latency. However, in a *post-hoc* regression analysis in which naming latency and recognition memory were entered as predictors of the priming measure, there was still some evidence of constraint on priming associated with naming latency (β for naming latency = .23, $p < .09$; β for recognition memory = .56, $p < .01$). That is, controlling for memory impairment as reflected in the recognition-memory measure, priming effects were still smaller in participants with very good baseline performance (lower latencies). This suggests that even in the slow fade-in condition there is some remaining constraint on priming in the fastest participants. This component of the priming variability, that is the component independently related to naming latency, was removed by linearly residualizing the (slow) priming measure. This new residualized priming measure is arguably a more sensitive measure of the priming study effect *per se*, that is, the least influenced by variability in naming latency. This measure was even more strongly related to hippocampal volume than was the unresidualized priming measure ($r = .41$, $p < .01$), and when predicted with the full set of anatomical measures the regression coefficient for the hippocampal volume was also .41 ($p < .05$), and no other measure contributed significantly.

DISCUSSION

Recognition Memory

These results suggest that recognition-memory performance is adversely affected by damage in several different sites. Consistent with earlier studies of patients with focal lesions (see Jernigan & Cermak, 1994 for review), we observed significant, independent effects of damage to the hippocampus and diencephalon. Damage to the amygdala/entorhinal region also contributed, independently of hippocampal damage. This result may be mediated by the effects of damage to the entorhinal and perirhinal cortex that is adjacent to the amygdala and is included in this region. Recent animal studies have more strongly implicated the entorhinal and perirhinal regions, than the amygdala, in memory functions (Meunier et al., 1996; Murray & Mishkin, 1998; Murray & Wise, 1996; Thornton et al., 1997; Wise et al., 1996). However, unfortunately, with these methods we cannot distinguish the effects of damage to these cortical regions from the effects of amygdalar damage *per se*.

Although damage to the striatum has been associated with memory impairment, particularly retrieval deficits, in the context of Huntington's disease (Butters et al., 1986), memory effects of nucleus accumbens damage *per se* have rarely been reported. No effect of striatal damage on recognition memory was observed in our previous anatomical study (Jernigan & Ostergaard, 1993). This may have been due to low power, or may have been because the accumbens was not measured separately in that study, but was partially included in the caudate and partially in the lenticular nucleus measure. It is possible that the accumbens effect observed here may reflect a specific role of the ventral striatum in the retrieval of visual word forms, or, alternatively, a role for this structure in stimulus evaluation or motivational requirements of the recognition-memory paradigm. Consistent with this is evidence that neurons in the ventral striatum respond differentially to stimuli associated with reinforcement, and to novel stimuli (Rolls, 1994). Animal studies of radial-maze performance suggest that while hippocampal/prefrontal interactions guide response selection when trial-specific, short-term memory is needed, the nucleus accumbens interacts with hippocampus in the production of

exploratory responses in novel situations (Floresco et al., 1997). Functions of the nucleus accumbens may modulate encoding operations in "test" situations, that is, when the subject is motivated by the desire to produce correct answers. Interestingly, a recent case report of a patient with selective damage to the nucleus accumbens revealed anterograde amnesia characterized by a tendency to produce false positives and intrusions on recognition-memory testing (Goldenberg et al., 1999).

With an increased sample size and greater anatomical variability, it has been possible in this study to detect the effects on recognition memory of damage in several regions that were not implicated in earlier studies. One interpretation of these results is that even performance on a relatively simple, yes/no recognition test, with unrelated distractors, depends on multiple processes within widespread neural operators. Damage affecting any of these components thus increases the severity of the recognition-memory impairment.

Naming Latency

Again consistent with the earlier results (Jernigan & Ostergaard, 1993), striatal damage was associated with increased naming latency. Effects of striatal damage on naming latency, however, unlike those on recognition memory, appeared to arise as a consequence of caudate, rather than nucleus accumbens damage. It is likely that the role of the more dorsally lying caudate in naming latency is related to the perceptual or lexical demands of the word-identification task. In a recent fMRI study (Desmond et al., 1998), activation of the caudate nucleus was associated with word retrieval in circumstances within which demands for response selection were high (i.e., when there were many correct exemplars). These results suggest that the role of caudate damage in naming impairments may be due to effects on the subjects' ability to select among the available lexical responses.

Interestingly, there was some evidence for an independent effect of mesial temporal lobe damage on naming latency. This can be predicted from the AI model, since the model assumes that, in order to identify the word, the subject uses whatever information is available in memory from all prior encounters with the word. Long-standing mesial temporal lobe damage could be expected to reduce the amount of such information available, and thus increase naming latency. However, one implication of this effect is that some subjects with baseline naming deficits, namely those with longer latencies due to mesial temporal lobe damage, may perform differently on priming tasks than others with longer latencies due, for example, to caudate damage. That is, subjects with poorer naming due to memory-encoding deficits (associated with mesial temporal lobe damage) will show less augmentation in their priming scores than will participants with impairment of naming due to other causes.

Priming

The regression results for the priming measures are also consistent with the results in Jernigan and Ostergaard (1993). As in that study, there was clear evidence for an effect of mesial temporal lobe damage on priming. In the previous study, there was an opposing effect of striatal damage on priming measures. This effect was considered to be mediated by the effect of the striatal damage on baseline performance. As expected, using the fade-in paradigm to reduce the baseline effect on priming also reduced the effect of striatal damage. However, examination of the anatomical regression results for the priming measure reveals a hint of the pattern observed previously. That is, the regression coefficients for the two striatal measures, though not approaching significance, have the opposite sign to that for the hippocampal measure, indicating that striatal damage was associated with higher priming. Interestingly, when the priming measure was residualized to further reduce the effects of naming latency, the coefficients for the striatal measures were further reduced to near zero.

In this study, as in the earlier anatomical study, there was again no evidence that occipital lobe damage resulted in perceptual priming deficits. This result provides no support for the conventional view that such priming effects represent intrinsic neocortical mechanisms within occipital lobe. However, the failure to demonstrate a significant effect of occipital lobe damage in no way establishes that such an effect does not exist. It is possible that only limited occipital lobe damage was present in the sample, or that the measure was not sufficiently specific to critical sites within occipital lobe.

General Discussion

The inclusion of clinically normal participants

It is unorthodox to include neurological patients and clinically normal participants together in studies of brain–behavior relationships; and this practice may raise concerns. Our assertion is that the most informative data sets for examining the relationship between behavioral deficits and degeneration in specific brain structures is one that includes individuals with widely ranging levels both of impairment and of brain degeneration. Correlative analyses within clinical groups, while common, are rarely conducted within data sets that meet this criterion. A particular concern that may arise is that the relationship between brain volumes and behavioral measures may be different within clinically normal participants than within the patients. The inclusion of clinically normal participants in this study was an attempt to add variability associated with age-related brain degeneration to that present due to disease factors within the smaller group of patients. It has been well established that brain volumes decline with age. We make the further assumption that decreasing brain vol-

umes, whether due to age or disease, are monotonically related to worsening performance. If this assumption is correct, then inclusion of aged normals with volume loss will contribute relevant variability. If it is not correct for control participants but it is for patients, then inclusion of aged normals will tend to obscure any relationships present within the patients, but it should not lead to spurious associations. We observe a number of strong associations between brain volumes and behavioral measures that we would be unlikely to detect if volume variability in normal-aged controls was unrelated to the behavioral measures.

These assertions notwithstanding, we have examined the brain–behavior relationships present within the clinically normal participants separately. Thirty-four of the participants of the present study were clinically normal. This is a rather small sample in which to conduct regression analyses with six independent variables. However, inspection of the regression results within the clinically normal participants reveals few discrepancies that are not consistent with the restriction of range that exists within this subsample on some of the variables. For example, the correlation between decreased hippocampal volume and poorer recognition memory is small and does not reach significance; however, this is consistent with substantial restriction of range on the recognition-memory measure and the fairly modest hippocampal losses noted in this group (see Figures 2 and 3). Interestingly, decreased nucleus accumbens volume was significantly correlated with poorer recognition-memory scores in this subsample, consistent with the substantial accumbens losses (equivalent to those observed in patients, see Figure 3) in some of the older normal participants of this study. Similarly, the fairly dramatic occipital cortex losses in older participants (Figure 3) resulted in significant specific associations between this measure and increased naming latency that did not reach significance in the full sample. In summary, inspection of the results within clinically normal participants suggested that when there was sufficient range on behavioral and anatomical measures, similar relationships were observed within this group to those observed in the larger group. Furthermore, there was evidence that inclusion of these participants had the desired effect of increasing the variability on some of the measures, and thereby revealing the presence of brain–behavior associations. It should be noted that Köhler et al. (1998), while observing an association between reduced hippocampal volumes and memory deficits in AD patients, observed an anomalous relationship between hippocampal volume and explicit-memory measures in normal subjects. This is a surprising result, for which the authors themselves have no explanation. We speculate that it may be related to selection bias that sometimes occurs in attempts to recruit very elderly controls for very elderly patients; that is, very elderly individuals who remain independent and willing to participate as controls may disproportionately be individuals protected to some extent from the functional consequences of brain atrophy by superior intellectual endowment.

Contamination of the priming measures by "explicit memory"

Findings, such as ours, of impaired priming in memory-impaired subjects, or of associations between priming measures and explicit-memory measures and indices of limbic system function, are sometimes attributed to "contamination" of the priming measure by explicit-memory processes. Specifically, there is the concern that slowing the appearance of the words may result in increased "contamination" of the priming measure. This concern has been addressed in detail by Ostergaard (Ostergaard, 1998, 1999). Briefly, a number of facts are inconsistent with the view that longer fade-in times result in increased conscious recollection. First, the response latencies observed in the slow fade-in task are shorter than response latencies observed in many priming tasks (such as word-fragment completion) on which amnesics are apparently normal and results from which have served as the basis for inferring the existence of a separate memory system. Second, the pattern of errors observed by Ostergaard (1999) in amnesics and controls gives no support to the contention that conscious retrieval was employed in the slow fade-in condition. Third, large increases in the priming effects were observed in the slow relative to the fast fade-in condition in amnesics as well as controls, and priming in the slow fade-in condition was as highly correlated with recognition-memory performance in amnesics as in controls. If the increase in priming effects and the association with recognition memory in the slow fade-in condition is due to the use of explicit memory, why are these effects at least as robust in the amnesics, who presumably have little or no explicit memory?

One might argue that if the priming measures produced in the fast and slow fade-in conditions were measures of separate forms of memory, with different neural bases, then the anatomical analysis of the priming measure obtained in the fast fade-in condition would suggest different anatomical correlates. *Post-hoc* anatomical analyses of the separate naming latency (baseline) and recognition-memory measures from the fast and slow fade-in conditions yielded virtually identical results to those presented in Table 2. However, when priming in the fast fade-in condition was predicted by the anatomical variables the results were different from those obtained when predicting priming in the slow condition (Table 2). No regression coefficient for any anatomical measure approached significance (e.g., the regression coefficient for the hippocampal measure was .01). This is consistent with our view that the priming measure obtained in the fast fade-in condition is strongly constrained by baseline performance and thus frequently grossly underestimates the real study effect. It is thus not a reliable measure of actual priming, and, not surprisingly, it shows no relationship with the condition of the brain.

Conclusions

Recognition-memory performance is affected independently by damage to the hippocampus and an adjacent re-

gion including amygdala, entorhinal, and perirhinal cortex, as well as by diencephalic damage and damage to the nucleus accumbens within the striatum. It is unlikely that damage in each of these sites affects recognition memory in the same way. Damage in some sites may affect memory processes *per se*, while damage in other sites may affect other processes of stimulus evaluation or response selection that play a role in recognition-memory performance. If this is the case, the implication is that damage in neural structures other than those with a primary role in memory may result in impaired recognition memory. In other words, under these circumstances, impaired recognition-memory performance can occur when memory is normal. This represents one means by which recognition performance could be "dissociated" from the level of actual memory function that exists.

With regard to the neural bases of priming deficits, several results of the present study are relevant. Damage to the caudate nucleus and to the hippocampus may contribute independently to performance deficits in word identification. Some impairments of word identification are associated with increased priming effects. Ironically, therefore, some damage to brain structures will, all other things being equal, result in larger priming scores. However, as earlier studies have shown, this occurs because of constraints on the priming effect that exist when performance on the priming task is determined primarily by the amount of relevant information available from sources other than that available from the study episode. This is most likely to be true when the subject has ready access, that is, can easily identify, a well-encoded (familiar) representation; in other words, when identification performance is very strong. Less access to perceptual or encoded lexical information, due either to experimental manipulations or to processing impairments secondary to cerebral damage, increases the subject's reliance on study information when processing the stimuli in the priming task. Priming measures obtained under these circumstances more accurately reflect variation in the amount of information remaining from the study episode. The results of this study suggest that this priming variability is correlated both with recognition-memory performance and with the integrity of structures within the mesial temporal lobe. By inference, these results imply that priming performance under the usual circumstances is, like recognition memory, affected by damage in multiple sites within the brain. The priming task, like the recognition-memory task, is likely to invoke several separate component processes, performance on each of which may contribute a component of the overall performance variability. In this case, damage in some sites has the effect of increasing the size of the priming effect, while damage in other sites leads to decreases in the size of the priming effect. Modification of the task to reduce the role of one or more of the component processes reduces the effects on performance variability of damage in structures that mediate those processes. Here, reducing the role that word-identification performance plays in the priming effect, relative to the role it played in the perceptual-

identification paradigm, reduced the effect of caudate damage on the priming measure.

In conclusion, we assert that dissociations between performance on explicit-memory tasks, such as recognition-memory tasks, and implicit-memory tasks, such as word priming, do not occur because two different kinds of memory (mediated by different neural structures) are measured with the different tasks. Rather, they occur because each of the tasks invokes a distinct set of component processes. These processes have separate neural bases, and each process contributes some variability to the overall performance variability on the task. It is our view that the word-priming task and the recognition-memory task for words share at least one processing component, namely that involving memory for words (i.e., encoding, consolidation, and/or retrieval), and it is likely that this accounts for the effects, observed here, of hippocampal damage on both recognition-memory impairment and priming impairment.

REFERENCES

Beauregard, M., Gold, D., Evans, A.C., & Chertkow, H. (1998). A role for the hippocampal formation in implicit memory: A 3-D PET study. *Neuroreport*, *9*, 1867–1873.

Brewer, J.B., Zhao, Z., Desmond, J.E., Glover, G.H., & Gabrieli, J.D. (1998). Making memories: Brain activity that predicts how well visual experience will be remembered [see comments]. *Science*, *281*, 1185–1187.

Buckner, R.L., Petersen, S.E., Ojemann, J.G., Miezin, F.M., Squire, L.R., & Raichle, M.E. (1995). Functional anatomical studies of explicit and implicit memory retrieval tasks. *Journal of Neuroscience*, *15*, 12–29.

Butters, N., Wolfe, J., Granholm, E., & Martone, M. (1986). An assessment of verbal recall, recognition and fluency abilities in patients with Huntington's disease. *Cortex*, *22*, 11–32.

Cermak, L., Talbot, N., Chandler, K., & Wolbarst, L. (1985). The perceptual priming phenomenon in amnesia. *Neuropsychologia*, *23*, 615–622.

Chiarello, C. & Hoyer, W.J. (1988). Adult age differences in implicit and explicit memory: Time course and encoding effects. *Psychology and Aging*, *3*, 358–366.

Chun, M.M. & Phelps, E.A. (1999). Memory deficits for implicit contextual information in amnesic subjects with hippocampal damage [see comments]. *Nature Neuroscience*, *2*, 844–847.

Cohen, N.J. & Squire, L.R. (1980). Preserved learning and retention of pattern-analyzing skill in amnesia: Dissociation of knowing how and knowing that. *Science*, *210*, 207–210.

Davis, H., Cohen, A., Gandy, M., Colombo, P., VanDusseldorp, G., Simolke, N., & Romano, J. (1990). Lexical priming deficits as a function of age. *Behavioral Neuroscience*, *104*, 288–297.

Desgranges, B., Baron, J.-C., & Eustache, F. (1998). The functional neuroanatomy of episodic memory: The role of the frontal lobes, the hippocampal formation, and other areas. *NeuroImage*, *8*, 198–213.

Desmond, J.E., Gabrieli, J.D., & Glover, G.H. (1998). Dissociation of frontal and cerebellar activity in a cognitive task: Evidence for a distinction between selection and search. *Neuroimage*, *7*, 368–376.

Elliott, R. & Dolan, R.J. (1998). Neural response during preference and memory judgments for subliminally presented stimuli: A functional neuroimaging study. *Journal of Neuroscience*, *18*, 4697–4704.

Floresco, S.B., Seamans, J.K., & Phillips, A.G. (1997). Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. *Journal of Neuroscience*, *17*, 1880–1890.

Gabrieli, J.D.E., Cohen, N.J., Huff, F.J., Hodgeson, J., & Corkin, S. (1984). Consequences of recent experiences with forgotten words in amnesia. *Society for Neuroscience Abstracts*, *10*, 383.

Gabrieli, J.D.E., Fleischman, D.A., Keane, M.M., & Reminger, S.L. (1995). Double dissociation between memory systems underlying explicit and implicit memory in the human brain. *Psychological Science*, *6*, 76–82.

Gabrieli, J.D.E., Milberg, W., Keane, M.M., & Corkin, S. (1990). Intact priming of patterns despite impaired memory. *Neuropsychologia*, *28*, 417–427.

Gardner, H., Boller, F., Moreines, J., & Butters, N. (1973). Retrieving information from Korsakoff patients: Effects of categorical cues and reference to the task. *Cortex*, *9*, 165–175.

Goldenberg, G., Schuri, U., Grömminger, O., & Arnold, U. (1999). Basal forebrain amnesia: Does the nucleus accumbens contribute to human memory? *Journal of Neurology, Neurosurgery and Psychiatry*, *67*, 163–168.

Grady, C.L., McIntosh, A.R., Horwitz, B., Maisog, J.M., Ungerleider, L.G., Mentis, M.J., Pietrini, P., Schapiro, M.B., & Haxby, J.V. (1995). Age-related reductions in human recognition memory due to impaired encoding. *Science*, *269*, 218–221.

Graf, P. & Schacter, D.L. (1985). Implicit and explicit memory for new associations in normal and amnesic subjects. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *11*, 501–518.

Graf, P., Squire, L.R., & Mandler, G. (1984). The information amnesic patients do not forget. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *10*, 164–178.

Hamann, S.B., Squire, L.R., & Schacter, D.L. (1995). Perceptual thresholds and priming in amnesia. *Neuropsychology*, *9*, 3–15.

Haxby, J.V., Horwitz, B., Maisog, J.M., Ungerleider, G.L., Mishkin, M., Schapiro, M.B., Rapoport, S.I., & Grady, C.L. (1993). Frontal and temporal participation in long-term recognition memory for faces: A PET-rCBF activation study. *Journal of Cerebral Blood Flow and Metabolism*, *13*(Suppl.1), S499.

Henke, K., Weber, B., Kneifel, S., Wieser, H.G., & Buck, A. (1999). Human hippocampus associates information in memory. *Proceedings of the National Academy of Sciences of the U.S.A.*, *96*, 5884–5889.

Hultsch, D.F., Masson, M.E., & Small, B.J. (1991). Adult age differences in direct and indirect tests of memory [published erratum appears in *Journal of Gerontology* 1991 Nov;46(6):P339]. *Journal of Gerontology*, *46*, 22–30.

Jacoby, L.L. & Witherspoon, D. (1982). Remembering without awareness. *Canadian Journal of Psychology*, *36*, 300–324.

Jernigan, T.L., Archibald, S.L., Berhow, M.T., Sowell, E.R., Foster, D.S., & Hesselink, J.R. (1991). Cerebral structure on MRI, Part I: Localization of age-related changes. *Biological Psychiatry*, *29*, 55–67.

Jernigan, T.L. & Cermak, L.S. (1994). Structural basis of memory. In A. Kertesz (Ed.), *Localization and neuroimaging in neuropsychology* (pp. 599–620). San Diego, California: Academic Press.

Jernigan, T.L. & Ostergaard, A.L. (1993). Word priming and recognition memory both affected by mesial temporal lobe damage. *Neuropsychology*, *7*, 14–26.

Jernigan, T.L., Ostergaard, A.L., Law, I., Svarer, C., Gerlach, C., & Paulson, O.B. (1998). Brain activation during word identification and word recognition. *Neuroimage*, *8*, 93–105.

Jernigan, T.L., Press, G.A., & Hesselink, J.R. (1990). Methods for measuring brain morphologic features on magnetic resonance images: Validation and normal aging. *Archives of Neurology*, *47*, 27–32.

Johnston, W.A., Dark, V.J., & Jacoby, L.L. (1985). Perceptual fluency and recognition judgements. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *11*, 3–11.

Kapur, N., Friston, K.J., Young, A., Frith, C.D., & Frackowiak, R.S. (1995a). Activation of human hippocampal formation during memory for faces: A PET study. *Cortex*, *31*, 99–108.

Kapur, S., Craik, F.I., Jones, C., Brown, G.M., Houle, S., & Tulving, E. (1995b). Functional role of the prefrontal cortex in retrieval of memories: A PET study. *Neuroreport*, *6*, 1880–1884.

Keane, M., Gabrieli, J.D.E., Fennema, A.C., Growdon, J.H., & Corkin, S. (1991). Evidence for a dissociation between perceptual and conceptual priming in Alzheimer's disease. *Behavioral Neuroscience*, *105*, 326–342.

Köhler, S., Black, S.E., Sinden, M., Szekely, C., Kidron, D., Parker, J.L., Foster, J.K., Moscovitch, M., Wincour, G., Szalai, J.P., & Bronskill, M.J. (1998). Memory impairments associated with hippocampal *versus* parahippocampal-gyrus atrophy: An MR volumetry study in Alzheimer's disease. *Neuropsychologia*, *36*, 901–914.

Light, L.L. (1991). Memory and aging: Four hypotheses in search of data. *Annual Review of Psychology*, *42*, 333–376.

Light, L.L. & Singh, A. (1987). Implicit and explicit memory in young and older adults. *Journal of Experimental Psychology: Learning, Memory, & Cognition*, *13*, 531–541.

Light, L.L., Singh, A., & Capps, J.L. (1986). Dissociation of memory and awareness in young and older adults. *Journal of Clinical and Experimental Neuropsychology*, *8*, 62–74.

Martin, A., Wiggs, C.L., & Weisberg, J. (1997). Modulation of human medial temporal lobe activity by form, meaning, and experience. *Hippocampus*, *7*, 587–593.

Meunier, M., Hadfield, W., Bachevalier, J., & Murray, E.A. (1996). Effects of rhinal cortex lesions combined with hippocampectomy on visual recognition memory in rhesus monkeys. *Journal of Neurophysiology*, *75*, 1190–1205.

Milner, B., Corkin, S., & Teuber, H.L. (1968). Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H.M. *Neuropsychologia*, *6*, 215–234.

Moscovitch, M., Kapur, S., Kohler, S., & Houle, S. (1995). Distinct neural correlates of visual long-term memory for spatial location and object identity—a positron emission tomography study in humans. *Proceedings of the National Academy of Sciences of the U.S.A.*, *92*, 3721–3725.

Murray, E.A. & Mishkin, M. (1998). Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. *Journal of Neuroscience*, *18*, 6568–6582.

Murray, E.A. & Wise, S.P. (1996). Role of the hippocampus plus subjacent cortex but not amygdala in visuomotor conditional learning in rhesus monkeys. *Behavioral Neuroscience*, *110*, 1261–1270.

Nyberg, L., Cabeza, R., & Tulving, E. (1996). PET studies of encoding and retrieval: The HERA model. *Psychonomic Bulletin & Review*, *3*, 135–148.

Ober, B.A. & Shenaut, G.K. (1988). Lexical decision and priming in Alzheimer's disease. *Neuropsychologia*, *26*, 273–286.

Ostergaard, A. (1999). Priming deficits in amnesia: Now you see them, now you don't. *Journal of the International Neuropsychological Society*, *5*, 175–190.

Ostergaard, A.L. (1994). Dissociations between word priming effects in normal subjects and patients with memory disorders: Multiple memory systems or retrieval? *Quarterly Journal of Experimental Psychology: Human Experimental Psychology*, *47A*, 331–364.

Ostergaard, A.L. (1998). The effects on priming of word frequency, number of repetitions, and delay depend on the magnitude of priming. *Memory and Cognition*, *26*, 40–60.

Ostergaard, A.L. & Jernigan, T.L. (1993). Are word priming and explicit memory mediated by different brain structures? In P. Graf & M.E.J. Masson (Eds.), *Implicit memory: New directions in cognition, development, and neuropsychology* (pp. 327–349). Hillsdale, New Jersey: Lawrence Erlbaum Associates.

Ostergaard, A.L. & Jernigan, T.L. (1996). Priming and baseline perceptual identification performance in amnesia: A comment on Hamann, Squire, and Schacter. *Neuropsychology*, *10*, 125–130.

Perruchet, P. & Baveux, P. (1989). Correlational analyses of explicit and implicit memory performance. *Memory and Cognition*, *17*, 77–86.

Polster, M., Nadel, L., & Schacter, D. (1991). Cognitive neuroscientific analyses of memory: A historical perspective. *Journal of Cognitive Neuroscience*, *3*, 95–116.

Rich, J.B., Bylsma, F.W., & Brandt, J. (1996). Item priming and skill learning in amnesia. *Journal of Clinical and Experimental Neuropsychology*, *18*, 148–158.

Rolls, E.T. (1994). Neurophysiology and cognitive functions of the striatum. *Revue Neurologique*, *150*, 8–9.

Salmon, D., Shimamura, A., Butters, N., & Smith, S. (1988). Lexical and semantic priming deficits in patients with Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology*, *10*, 447–494.

Schacter, D.L. (1990). Perceptual representation systems and implicit memory: Toward a resolution of the multiple memory systems debate. In A. Diamond (Ed.), *The development and neural bases of higher cognitive function, Vol. 608* (pp. 543–571). New York: The New York Academy of Sciences.

Schacter, D.L. (1991). Consciousness and awareness in memory and amnesia: Critical issues. In D. Milner & M. Ruggs (Eds.), *Neuropsychology of consciousness* (pp. 180–200). London: Academic Press.

Schacter, D.L. (1992). Priming and multiple memory systems: Perceptual mechanisms of implicit memory. *Journal of Cognitive Neuroscience*, *4*, 244–256.

Schacter, D.L., Alpert, N.M., Savage, C.R., Rauch, S.L., & Albert, M.S. (1996). Conscious recollection and the human hippocampal formation: Evidence from positron emission tomography. *Proceedings of the National Academy of Sciences of the U.S.A.*, *93*, 321–325.

Schacter, D.L. & Church, B. (1995). Implicit memory in amnesic patients: When is auditory priming spared? *Journal of the International Neuropsychological Society*, *1*, 434–442.

Schacter, D.L., Church, B., & Bolton, E. (1995). Implicit memory in amnesic patients: Impairment of voice-specific priming. *Psychological Science*, *6*, 20–25.

Schacter, D.L., Cooper, L.A., & Valdiserri, M. (1992). Implicit and explicit memory for novel objects in older and younger adults. *Psychology and Aging*, *7*, 299–308.

Shallice, T., Fletcher, P., Frith, C.D., Grasby, P., Frackowiak, R.S., & Dolan, R.J. (1994). Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature*, *368*, 633–635.

Shimamura, A.P. & Squire, L.R. (1984). Paired-associate learning and priming effects in amnesia: A neuropsychological study. *Journal of Experimental Psychology: General*, *113*, 556–570.

Smith, M. & Oscar-Berman, M. (1990). Repetition priming of words and pseudowords in divided attention and in amnesia. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *16*, 1033–1042.

Squire, L.R. (1992). Declarative and nondeclarative memory: Multiple brain systems supporting learning and memory. *Journal of Cognitive Neuroscience*, *4*, 232–243.

Squire, L.R., Knowlton, B., & Musen, G. (1993). The structure and organization of memory. *Annual Review of Psychology*, *44*, 453–495.

Squire, L.R., Ojemann, J.G., Miezin, F.M., Petersen, S.E., Videen, T.O., & Raichle, M.E. (1992). Activation of the hippocampus in normal humans: A functional anatomical study of memory. *Proceedings of the National Academy of Sciences of the U.S.A.*, *89*, 1837–1841.

Squire, L.R., Shimamura, A.R., & Graf, P. (1987). Strength and duration of priming effects in normal subjects and amnesic patients. *Neuropsychologia*, *25*, 195–210.

Stern, C.E., Corkin, S., González, R.G., Guimaraes, A.R., Baker, J.R., Jennings, P.J., Carr, C.A., Sugiura, R.M., Vedantham, V., & Rosen, B.R. (1996). The hippocampal formation participates in novel picture encoding: Evidence from functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences of the U.S.A.*, *93*, 8660–8665.

Thornton, J.A., Rothblat, L.A., & Murray, E.A. (1997). Rhinal cortex removal produces amnesia for preoperatively learned discrimination problems but fails to disrupt postoperative acquisition and retention in rhesus monkeys. *Journal of Neuroscience*, *17*, 8536–8549.

Tulving, E. (1985). How many memory systems are there? *American Psychologist*, *40*, 385–398.

Tulving, E., Kapur, S., Craik, F.I., Moscovitch, M., & Houle, S. (1994a). Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings [see comments]. *Proceedings of the National Academy of Sciences of the U.S.A.*, *91*, 2016–2020.

Tulving, E., Kapur, S., Markowitsch, H.J., Craik, F.I., Habib, R., & Houle, S. (1994b). Neuroanatomical correlates of retrieval in episodic memory: Auditory sentence recognition [see comments]. *Proceedings of the National Academy of Sciences of the U.S.A.*, *91*, 2012–2015.

Tulving, E. & Schacter, D.L. (1990). Priming and human memory systems. *Science*, *247*, 301–306.

Verfaellie, M., Cermak, L.S., Letourneau, L., & Zuffante, P. (1991). Repetition effects in a lexical decision task: The role of episodic memory in the performance of alcoholic Korsakoff patients. *Neuropsychologia*, *29*, 641–657.

Wagner, A.D., Schacter, D.L., Rotte, M., Koutstaal, W., Maril, A., Dale, A.M., Rosen, B.R., & Buckner, R.L. (1998). Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity [see comments]. *Science*, *281*, 1188–1191.

Warrington, E.K. & Weiskrantz, L. (1968). New method of testing long-term retention with special reference to amnesic patients. *Nature*, *217*, 972–974.

Wiggs, C.L., Weisberg, J., & Martin, A. (1999). Neural correlates of semantic and episodic memory retrieval. *Neuropsychologia*, *37*, 103–118.

Wise, S.P., Murray, E.A., & Gerfen, C. R. (1996). The frontal cortex-basal ganglia system in primates. *Critical Reviews in Neurobiology*, *10*, 317–356.