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Functional neuroanatomy of human declarative memory

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by

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DEDICATION

I dedicate this work to my family, friends, and colleagues. To my parents, thank you for your love, support, and faith in my abilities. To my uncles and aunts with strategically located houses in Los Angeles and Davis, thank you for letting me interrupt your lives for months (and years) on end. To my friends, thank you for laughing even when the jokes weren't funny. To the members of the Squire lab past and present, thank your for showing me the ropes, correcting my mistakes, and laughing even when the jokes weren't funny. To Jen Frascino, thank you for doing all the work, taking none of the credit, and saving me a table at Del Mar. To Sherry Hargrove, thank you for fixing all the problems before I even knew there were problems. Most of all, to Larry Squire, thank you for your wisdom, patience, friendship, patience, advice, patience, direction, and patience.

J.J.G.

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ABSTRACT OF THE DISSERTATION

Functional neuroanatomy of human declarative memory

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It is widely accepted that the medial temporal lobe (MTL) and related structures in the diencephalon play a critical role in declarative memory, which is conscious knowledge about facts and events. A fundamental question is whether there are divisions of labor of declarative memory function within the MTL or diencephalon. In one view, specific declarative memory functions (e.g., recognition memory for items) depend on some regions of the MTL and diencephalon but are

entirely independent of other regions. In another view, each region of the MTL and diencephalon is important for all declarative memory functions. To address this issue, we assessed the location and extent of brain damage in memory-impaired patients using post-mortem histology and compared the effects of lesions to the MTL or diencephalon on memory performance. Next, we assessed the location and extent of brain damage in living, memory-impaired patients using structural MRI and administered memory tests to patients with damage limited to the hippocampal region. Finally, we used functional neuroimaging to study brain activity in healthy participants performing recognition memory tasks. We report that damage to the MTL or diencephalon produces a common amnesic syndrome with impaired declarative memory (anterograde and retrograde memory) but sparing of nondeclarative memory and other cognitive functions. Further, we report that proposed dichotomies between item memory and associative memory or item memory and source memory do not capture the division of labor of declarative memory function in the MTL and diencephalon. Our findings suggest that each region of the MTL and related regions of the diencephalon play an important role in all declarative memory function.

I. INTRODUCTION

Functional neuroanatomy is the study of the link between brain function and brain structure. The origin of "modern" functional neuroanatomy may be the famous 1848 account of Phineas Gage, a railroad worker who suffered brain damage to the frontal lobes when a steel rod was driven through his head (Harlow, 1848). That Gage survived the injury was remarkable, but equally notable was the dramatic change in his personality. Before the injury Gage had been energetic and affable, but after the injury he was described as lazy and profane. Friends and family reported that Gage was "no longer Gage." These observations lead to speculation that the frontal lobes are involved in rational decision-making, social behavior, and the processing of emotion (e.g., Damasio et al., 1994).

Many credit the French physician Paul Pierre Broca with the first demonstration that a specific brain function would be localized to a specific region of the cortex (Broca, 1861). Using post-mortem analysis of the brains of neurological patients (most notably the patient Tan), Broca discovered that damage to the third frontal convolution on the left side of the brain produced non-fluent aphasia. Thus, this brain region was thought to be involved in the production of language.

Modern study of the functional neuroanatomy of human memory began with the famous patient HM (Scoville & Milner, 1957). In 1953, HM received an experimental surgical intervention (bilateral medial temporal lobe resection) to relieve intractable temporal lobe epilepsy. The surgery successfully relieved his seizures, and

HM did not experience any changes in personality (like Gage) or problems with language (like Tan). He performed well on tests of perception, intelligence, and reasoning. However, it was clear that HM had a severe memory impairment (amnesia). HM seemed only vaguely aware of his operation, wasn't able to remember events only minutes after they occurred, and was unable to recognize the doctors and nurses who came to see him several times a day. Further, he was unable to remember some things that had occurred before the surgery, although he could recall memories from his childhood. These observations suggested that part of the brain removed during the surgery was important for forming new memories and remembering past experiences.

HM had severe anterograde and retrograde memory impairments (Scoville & Milner, 1957; Corkin, 2002). It was noted, however, that HM was capable of certain kinds of learning. For example, Milner (1962) had HM practice tracing a star while looking in a mirror. HM (like controls) initially made many errors, but he eventually he learned the skill of "mirror drawing". Notably, he learned the skill as quickly as healthy controls. However, shortly after the testing session HM could not consciously remember that he had ever practiced mirror drawing. Observations such as these in HM and other patients led to the conclusion that memory is not a unitary phenomenon, but rather is made up of many different abilities (Cohen & Squire, 1980; Zola-Morgan & Squire, 1988; Squire, 1992; Squire & Knowlton, 1999). Further, these observations suggested that different regions of the brain are important for different memory abilities.

HM was not the first neurological patient to suffer from memory impairment. For example, the Russian physician S.S. Korsakoff described a syndrome of memory impairment in neurological patients that was especially prevalent among chronic alcoholics (Korsakoff, 1887). Around that time, post-mortem neuropathological investigation found that damage to the diencephalon (including the mammillary nuclei and the thalamus) was common in patients with "Korsakoff's syndrome", but no consensus about the particular lesion associated with memory loss was reached (for review, see Victor et al., 1989).

It should be noted that damage to the MTL or diencephalon can result in memory impairment regardless of the means by which the damage occurs (for review, see Mayes, 1988). HM's medial temporal lobes were surgically removed, but MTL damage can also result from many other causes (e.g., cerebral ischemia, herpes simplex infection). Similarly, in addition to Korsakoff's syndrome (which classically results from thiamine deficiency), stroke and direct trauma (as in the case of the famous patient NA) can cause diencephalic damage (Teuber et al., 1968; Squire & Moore, 1979; Victor et al., 1989). As we will see in Chapter II, damage to the MTL and damage to the diencephalon produce remarkably similar memory impairments.

Memory systems

The type of memory impaired in patient HM (and in patients with Korsakoff's syndrome) is declarative (or explicit) memory, which is conscious knowledge about facts and events (Squire, 1992; Squire & Knowlton, 1999). The ability to answer the

question, “Who was the first president of the United States?” is an example of declarative memory. Specifically, this ability is an example of recall memory, the ability to reproduce an item from memory. Another example is the ability to select “George Washington” from a list of possible answers. Specifically, this ability is an example of recognition memory, the ability to judge an item as previously encountered. Recognition memory is a particularly well-studied example of declarative memory and will be discussed at greater length elsewhere in Chapter I.

Qualitatively, memories for events (episodic memories) are characterized by the ability to mentally replay the event (i.e., mentally time travel) and are specific for a certain time and place (e.g., Tulving, 1983). Memories for facts (semantic memories) are experienced as context-free knowledge not associated with any specific time or place. Finally, declarative memory is highly adaptable in the sense that the expression of knowledge is not limited to the context in which it was learned, and the response (e.g., answer) can be given in a variety of ways (e.g., spoken, written).

Declarative memory can be contrasted with nondeclarative (or implicit) memory, which refers to a group of abilities, skills, biases, and preferences that are the result of experience but are functionally and neuroanatomically distinct from declarative memory (Squire & Zola-Morgan, 1988; Squire, 1992; Squire & Knowlton, 1999). Examples of nondeclarative memory include motor learning (e.g., mirror tracing or riding a bicycle), classical conditioning, and the phenomenon of priming. (For more examples of nondeclarative memory, see Chapter II.) Whereas declarative memory involves conscious knowledge, nondeclarative memory can be exhibited

unconsciously (i.e., occur outside of awareness). Where declarative memory is adaptable, nondeclarative memory can only be expressed through performance of a stereotyped behavior. Most importantly, declarative memory and nondeclarative memory depend on separate brain structures.

The neuroanatomy of declarative memory

As noted above, declarative memory in patient HM was severely impaired following surgical removal of a region of his brain known as the medial temporal lobe (MTL). The MTL consists of the hippocampus (dentate gyrus and CA fields), the subicular complex, and the cortices of the parahippocampal gyrus (perirhinal, entorhinal, and parahippocampal cortices) (Squire et al., 2004; Lavenex & Amaral, 2000; Burwell et al., 1996). The amygdala was also removed. Following HM's surgery and the diagnosis of his memory impairment, it was unclear which of these regions was critical for memory.

Extensive work has been carried out to understand the anatomy of the MTL and diencephalon. This work has revealed extensive interconnections between these two brain regions. A brief description of the neuroanatomy of memory-related structures in the MTL and diencephalon follows (for a more extensive review, see Jones, 1985; Insausti et al., 1987; Markowitsch, 1988; Amaral & Insausti, 1990; Suzuki & Amaral, 1994; Suzuki & Amaral, 2004; Aggleton et al., 2005).

Much of the input to the MTL comes into parahippocampal cortex and perirhinal cortex from the frontal, temporal and parietal lobes and the insular and

cingulate cortices. Most of the input to perirhinal cortex comes from the ventral "what" stream, whereas most of the input to parahippocampal cortex comes form the dorsal "where" stream. These structures mainly project to entorhinal cortex, which then projects mainly into the hippocampus (via the so-called perforant path). The hippocampus has several outputs including a projection back to entorhinal cortex and a projection to the mammillary nuclei in the diencephalon via the fornix. The mammillary nuclei project mainly to the anterior nuclei of the thalamus (including the anteroventral and anteromedial nuclei) via the mammillothalamic tract. Perirhinal cortex and the amygdala send projections directly to the mediodorsal nucleus of the thalamus via the ventral amygdalofugal pathway. The thalamic nuclei have diverse projections to neocortex and subcortical structures, including some fibers that project from the anterior nuclei back to cingulate cortex and then back to the hippocampus (the so-called Papez circuit).

Determining brain damage in memory-impaired patients

Much of the present work relies critically on our ability to determine the location and extent of brain damage in memory-impaired patients. To make confident statements about hippocampal function from the study of memory-impaired patients, we must be certain that the patients under study have damage limited to the hippocampal region. (The same applies regardless of the brain region being studied.) A discussion of two methods that have been used to determine the location and extent of brain damage in memory-impaired patients follows.

Definitive statements about brain damage cannot be made without detailed, post-mortem, histological analysis. Such studies of patients with well-characterized memory impairments are rare. Knowledge of the role of the medial temporal lobe in human memory has been greatly advanced by the study of patient RB (Zola-Morgan et al., 1986) and patients GD, LM, and WH (Rempel-Clower et al., 1996). Neurohistological examination revealed that RB and GD became amnesic due to a bilateral lesion limited to the CA1 field of the hippocampus. LM became amnesic due to bilateral damage to all of the CA fields of the hippocampus, the dentate gyrus, and the entorhinal cortex. Neurohistological examination of WH revealed a bilateral lesion to all of the CA fields of the hippocampus, the dentate gyrus, the subicular complex, and the entorhinal cortex.

Similarly, knowledge of the role of the diencephalon in human memory has been greatly aided by the study of patients with Korsakoff's syndrome, including the study of patients EA and HJ (Mair et al., 1979) and patients JW and BC (Mayes et al., 1988). All of these patients were reported to have damage to the mammillary nuclei. Further, in all of these patients a "band of gliosis" was reported anteromedial to the mediodorsal nucleus of the thalamus in the region of the paratenial nucleus, although this conclusion has come under debate (see Chapter II).

In Chapter II, we report our findings from post-mortem, histological analysis of three patients with well-characterized memory impairments. Uniquely, we report findings from a patient with damage to the MTL and patients with damage to the diencephalon who all took some of the same neuropsychological memory tests during

life. Histological analysis as undertaken in Chapter II and in the studies described above is not feasible is most cases. The obvious limitation is that histological analysis cannot be used to assess brain damage in living patients. Nevertheless, detailed neuroanatomical descriptions of the location and extent of brain damage are critical to the study of the functional neuroanatomy of human memory. We address the assessment of brain damage in living patients in Chapter III.

Advances in neuroimaging (most notably magnetic resonance imaging, or MRI) have made the assessment of brain damage in living, memory-impaired patients possible (e.g., Squire et al., 1989; Press et al., 1989; Squire et al., 1990). Some brain regions (e.g., the hippocampus) are easily visualized with neuroimaging. Other regions (e.g., perirhinal, entorhinal, and parahippocampal cortex) are difficulty to distinguish because cytoarchitectural characteristics are not evident on MRI.

To address this problem, Insausti et al. (1998a, 1998b) studied 44 nonpathologic brains and determined landmarks for perirhinal, entorhinal, and parahippocampal cortex that can be seen on MRI. Using these landmarks, it is possible to estimate the volume of perirhinal, entorhinal, and parahippocampal cortex. Thus, it is possible to determine whether these brain regions are damaged by comparing the volume of these regions in controls to the volume of these regions in patients.

One difficulty with this approach has been that the volume of these brain regions varies widely even in the healthy population. It is thought that the volume of brain regions varies with the overall volume of the brain. Thus, most attempts to use

MRI volumetry to measure the volume of brain regions involve some correction for overall brain size. In Chapter III, we assess the utility of three of these different methods for correcting measurements of the volume of the MTL for overall brain size.

For the present work, we have assessed brain damage in memory-impaired patients in one of two ways. In deceased patients, we assessed brain damage using post-mortem histology (Chapter II). In living patients, we assessed brain damage using MRI volumetry (Chapter III). In the living patients we determined that damage was limited mainly to the hippocampal region (dentate gyrus, CA fields, and the subiculum), with little or no volume reduction evident in the rest of the MTL or in the other lobes of the brain (Chapter III, Gold & Squire, 2005; Bayley et al., 2005). Thus, we studied the role of the hippocampus in human memory by administering memory tests to these patients and patients with similar brain damage. In Chapter IV and Chapter V, we address the role of the hippocampus in recognition memory.

Recognition memory

Recognition memory is the ability to the judge a previously encountered item as familiar (item memory). Item memory can occur along with knowledge about the episode in which the item was encoded (source memory), or item memory can involve simply knowing that an item was presented with no knowledge about the encoding episode. Item memory in the absence of source memory is sometimes referred to as "familiarity", while item memory along with source memory is sometimes referred to as "recollection" (Mandler, 1980; Yonelinas, 2002). It has been suggested that item

memory in the absence of source memory depends importantly on perirhinal cortex, and item memory along with source memory depends importantly on the hippocampus (Brown & Aggleton, 2001; Yonelinas et al., 2002; Davachi et al., 2003; Ranganath et al., 2003; but see Manns et al., 2003; Wixted & Squire, 2004; Wais et al., 2006). We address this hypothesis in Chapter V.

It has also been proposed that the hippocampus is particularly important for associative memory, which is memory for the relationship between items (e.g., Kroll et al., 1997; Giovanello et al., 2003). In this view perirhinal cortex is important for establishing the neural representation of each individual item, and the hippocampus is only important for binding these representations together. We address this hypothesis in Chapter IV.

Functional neuroimaging

Much has been learned about the functional neuroanatomy of human memory from the study of patients with brain damage to memory-related structures. Recently, functional neuroimaging (and specifically functional magnetic resonance imaging, or fMRI) has made it possible to measure activity in the brains of healthy subjects performing memory tasks. A brief description of fMRI and its uses in studying the functional neuroanatomy of declarative memory follows (for a more extensive review, see Buxton, 2002).

Functional MRI measures brain activity indirectly through the analysis of blood oxygen level dependent (BOLD) signal changes. Briefly, when an area of the

brain (e.g., the hippocampus) becomes active, it draws more oxygen out of the blood and into tissue. This creates a local, temporary drop in the oxygen saturation of the blood. In response to this drop, blood flow to the active region increases, resulting in higher-than-normal oxygen saturation. MR signal increases in regions of high oxygen saturation relative to regions with low oxygen saturation, probably due to the paramagnetic properties of hemoglobin (Buxton, 2002). Thus, when a brain region becomes active, the MR signal in that region will show a series of changes related to blood flow called the hemodynamic response.

One useful method for addressing the functional neuroanatomy of memory using fMRI has been the subsequent memory paradigm (Paller & Wagner, 2002). In this paradigm, brain activity is measured with fMRI while volunteers study a list of items. Outside of the scanner, participants take a memory test for the items they studied in the scanner. Brain activity associated with items that were later remembered can then be compared to brain activity associated with items were later forgotten. Brain regions that are important for encoding new memories would be expected to show a different pattern of activity for items that were later remembered than items that were later forgotten. See Chapter V for more details about fMRI and the subsequent memory paradigm.

Functional MRI is purely a correlative technique; that is, fMRI cannot demonstrate that a certain brain region is necessary for a certain function, only that activity in a certain region is correlated with a certain function (Squire et al., 2004). In contrast, studies of patients with brain damage can provide evidence that a certain

brain region is necessary for a certain function. It seems logical that these two techniques should be used in conjunction to reach confident conclusions about brain function, but this has been done only rarely (Giovanello et al., 2003; Giovanello et al., 2004; Bor et al., 2006). Thus, in Chapter V, we carried out an fMRI study in healthy controls and a parallel study using the same memory test in patients with damage limited to the hippocampal region.

Summary

In the following chapters, we investigate the functional neuroanatomy of human declarative memory. In Chapter II, we assess the location and extent of brain damage in deceased patients using neurohistology. These patients took part in extensive neuropsychological memory testing during life. We report that damage to the MTL or diencephalon causes a common phenotype of memory impairment that includes impairment in declarative memory function. In order to address the functional neuroanatomy of declarative memory in living patients, we need to quantify the location and extent of brain damage using neuroimaging. In Chapter III, we use MRI volumetry to characterize brain damage in living, memory-impaired patients. We report that damage in a group of patients is limited mainly to the hippocampal region. Next, we administer memory tests to these patients and patients with similar brain damage to determine whether the hippocampal region is involved in specific declarative memory functions. In Chapter IV, we address the role of the hippocampal region in item memory and associative memory. In Chapter V, we address the role of

the hippocampal region in item memory and source memory. Further, we assessed brain activity in healthy participants during the encoding period of an item memory and source memory task. Finally, we conclude that simple dichotomies (e.g., item memory and associative memory, item memory and source memory) do not capture the division of labor of memory function in the MTL or diencephalon.

II. NEUROPSYCHOLOGICAL AND NEUROPATHOLOGICAL ASSESSMENT OF MEMORY IMPAIRMENT FOLOWING DAMAGE TO THE MEDIAL TEMPORAL LOBE OR DIENCEPHALON

A. ABSTRACT

Much of our knowledge about the functional neuroanatomy of human memory has been learned from the study of patients with brain damage to memory-related structures. Most useful are reports that combine extensive neuropsychological memory testing and detailed post-mortem neuropathological investigation for the same patients. Such reports are rare. We present the results of neuropsychological memory testing and neuropathological investigation for three patients: one with damage to the medial temporal lobe, one with diencephalic damage due to alcoholic Korsakoff's syndrome, and one with diencephalic damage due to bithalmic thalamic infarction. All three participated in many of the same studies of declarative and nondeclarative memory function. We report that damage to the medial temporal lobe or diencephalon produces a common amnesic syndrome that is characterized by impairment of declarative memory (anterograde and retrograde) and normal performance on tests of nondeclarative memory and tests of other cognitive functions. Importantly, we report that recognition memory is impaired in all three patients.

B. INTRODUCTION

Declarative memory, conscious knowledge about facts and events, depends on structures within the medial temporal lobe (MTL), including the hippocampus (dentate gyrus and CA fields), subicular complex and the adjacent perirhinal, entorhinal and parahippocampal cortices (Burwell et al., 1996; Lavenex & Amaral, 2000; Squire et al., 2004). The MTL has extensive connections to the diencephalon, and thus damage to the diencephalon produces memory impairment that is strikingly similar to the memory impairment produced by damage to the MTL (e.g., Victor et al, 1989; Aggleton & Brown, 1999). Damage to either the MTL or diencephalon produces a syndrome of amnesia characterized by impairment of anterograde and retrograde declarative memory without impairment of nondeclarative memory or other cognitive functions (e.g., Mayes, 1988; Squire, 1992; Squire et al., 2004).

It has been shown that damage limited to the CA1 field of the hippocampal region is sufficient to cause significant memory impairment in humans (Zola-Morgan et al., 1986; Rempel-Clower et al., 1996). Further, more extensive damage to the hippocampus or MTL is associated with more profound memory impairment (Rempel-Clower et al., 1996). Work with experimental animals has reached similar conclusions (for review, see Squire et al., 2004).

There has been great interest in the determination of the critical lesion for memory loss in patients with diencephalic damage. Previous reports of diencephalic amnesia have emphasized the role of the mediodorsal thalamic nucleus (MD, Victor et al., 1989), anterior thalamic nuclei (Harding et al., 2000), paraventricular thalamic nuclei (Mair et al., 1979; Mayes et al., 1988), mammillothalamic tracts (Van der Werf

et al., 2000; Yoneoka et al., 2004) and the internal medullary lamina (Markowitsch, 1988), and the mammillary nuclei (Vann & Aggleton, 2004). Some have also suggested that a lesion must include more than one of these structures to produce profound memory impairment (Mayes et al., 1988; Graff-Radford et al., 1990; Kopelman, 1995; Vann & Aggleton, 2004).

Much of the evidence about the neuroanatomical basis of diencephalic amnesia in humans comes from the study of Korsakoff's syndrome using radiology (e.g., Shimamura et al., 1988; Squire et al., 1990; Colchester et al., 2001) or post-mortem neurohistology (Victor et al., 1989; Mair et al., 1979; Mayes et al., 1988; Harding et al., 2000). In addition, there have been radiological studies of memory impairment as a result of diencephalic infarction (von Cramon et al., 1985; Graff-Radford et al., 1990; Van der Werf et al., 2000; Van der Werf et al., 2003; Yoneoka et al., 2004) or trauma (Squire et al., 1989). To our knowledge, the present study the first to report post-mortem neurohistological findings from a patient with well-characterized memory impairment as the result of diencephalic infarction. Note that although the term "Korsakoff's syndrome" can be used to describe any case of memory impairment as a result of brain damage, we will limit our use of the term to cases of memory impairment as a result of diencephalic damage secondary to chronic alcoholism (see Mayes et al., 1988).

The most informative reports about the functional neuroanatomy of human memory include both extensive neuropsychological findings and post-mortem neurohistology findings from the same patients. To our knowledge, only four patients

with memory impairment as a result of medial temporal lobe amnesia (RB, Zola-Morgan et al., 1986; GD, LM, WH, Rempel-Clower et al., 1996) and four patients with memory impairments as a result of diencephalic damage due to Korsakoff's syndrome (EA and HJ, Mair et al., 1979; BC and JW, Mayes et al., 1988) have been reported. To our knowledge, the present study is the first to report extensive neuropsychological findings and post-mortem neurohistological findings from a patient with amnesia due to MTL damage and patients with amnesia due to diencephalic damage who took the same memory tests.

We report neuropsychological and post-mortem neurohistological findings from three patients. One patient (NC) had damage to the MTL. Two patients (MG and PN) had damage to diencephalic structures due to bilateral thalamic infarction or Korsakoff's syndrome, respectively. We discuss findings from these patients and the implications for our understanding of the functional neuroanatomy of memory.

C. MATERIALS AND METHODS

Three amnesic patients (NC, MG, and PN) were studied for 7 to 21 years. Their case histories are described below.

Patient NC

Case history. Patient NC was a left-handed, Caucasian female born in 1943. She received 12 years of education and subsequently worked as a nurse's aid for ten years. NC reported at least a 14-year history of alcoholism, although at autopsy her

liver showed no signs of cirrhosis. She was not known to have drunk alcohol from 1982 to 1994, the period during which she participated in studies in our laboratory. NC had a history of smoking cigarettes (a pack per day for at least 25 years). She was prescribed metoprolol, propranolol, and nitrostat for severe hypertension and angina, but these conditions remained uncontrolled.

NC's psychiatric history is remarkable for childhood hospitalizations for "crazy" behavior. She received a diagnosis of schizo-affective disorder with paranoid-type schizophrenia symptoms and depressive mood disorder. She saw a psychiatrist regularly and controlled the disorder with, among other treatments, trazadone and doxepin.

Her neurological history is remarkable for a seizure disorder that she controlled with Dilantin and a history (self-reported) of frequent head trauma. NC's neurological history is also remarkable for mild distal polyneuropathy likely related to alcohol abuse, weak right extensor planar responses, "wild" right arm drift, and left facial weakness. She received a diagnosis of sleep apnea shortly before her death.

In 1979, at the age of 36, NC was diagnosed with a severe memory disorder, initially identified as Korsakoff's syndrome. At the time she was also noted to have poor performance on digit span and on a calculation task. These difficulties were attributed to attention problems, possibly due to her medications. Her memory impairment remained stable during the 12 years that we tested her. We now suggest that the initial diagnosis of Korsakoff's syndrome was incorrect, as our histological

analysis (see Results) revealed bilateral damage to the hippocampal formation in the absence of diencephalic damage.

In 1992, NC experienced an episode of congestive heart failure accompanied by a small, subendocardial infarction. She was subsequently diagnosed with hypertensive cardiomyopathy. In January, 1994, she was hospitalized for pneumonia and later discharged. One month later, she was found deceased in her board-and-care facility. She was 51 years old. The cause of death was reported as coronary artery disease, including near-complete occlusion of the left anterior descending and right coronary arteries. An autopsy revealed hepatic and pulmonary congestion, as well as arteriolar nephrosclerosis.

Acquisition and preparation of tissue. NC's death was unattended, so the exact interval between death and removal of the brain is unknown (4 to 10 hours). The brain was placed in cold 10% formalin in 0.1M phosphate buffer for 3 months. Photographs of the whole brain were taken, and then the brain was cut into ~1-cm-thick coronal blocks. Each block was photographed and inspected. Blocks were then returned to cold 10% formalin in 0.1M phosphate buffer for 2 months. The blocks were then placed in a cryoproctectant solution of 10% glycerin and 10% formalin in 0.1M phosphate buffer. After 2 days, the blocks were moved into a cryoproctectant solution of 20% glycerin and 10% formalin in 0.1M phosphate buffer for 2 months. Then, whole coronal blocks were frozen between glass slides by placing them in -70^{o}C isopentene for 45 min and stored at -70^{o}C.

Patient MG

Case history. MG was a right-handed, Caucasian female born in 1932. MG had a history of cigarette smoking (approximately 1.5 packs per day for as long as 30 years) with no history of alcohol use. She had carotid artery occlusive disease, severe hypertension and angina controlled with clonidine and nifedipine, and a history of depression for which she variously took perphenazine, trazadone, and nortriptyline. Her neurological history is further significant for transient ischemia attacks (TIA's) that resulted in fainting spells.

In 1985, MG underwent bilateral carotid and femoral endarterectomy. In 1986, she was admitted to the hospital where an MRI revealed a symmetric, bi-thalamic stroke. At that time, she was noted to have significant anterograde memory loss. She participated in our studies from 1987 to 1994.

In June, 1994, angiography revealed at least 50% carotid blockage bilaterally, worse on the right. Head CT revealed evidence of small vessel white matter disease and a new, non-hemorrhagic infarct dating to the recent six months. Importantly, she was noted to have no musculoskeletal abnormalities at this time.

On Dec. 12, 1996, MG was admitted to the hospital with acute and chronic renal failure, urinary tract infection, and dehydration. After treatment she was noted to be ambulatory with a walker, but showing a "contracted left upper extremity". MG was released from the hospital but returned two weeks later in acute respiratory distress. She was intubated and ventilated. Examination revealed impending gangrene of the left lower leg due to obstruction of the iliac artery. At this time she

also had left hemiparesis and a deformed left hand. These findings suggest that she had had a new, right-sided stroke, likely dating to the hospitalization of Dec. 12. Honoring MG's "do not resuscitate" order, her family requested extubation and death supervened. She was 64 years old.

Acquisition and preparation of tissue. Approximately 4 hours after death, the brain was removed and immediately placed in cold 10% formalin in 0.1M phosphate buffer for 54 months. In June, 2001, photographs of the whole brain were taken, and then the brain was cut into ~1-cm-thick coronal blocks. Blocks were then returned to cold 10% formalin in 0.1M phosphate buffer for 1 month. Each block was then photographed and the blocks were placed in a cryoproctectant solution of 10% glycerin and 10% formalin in 0.1M phosphate buffer. After 4 days, the blocks were moved into a cryoproctectant solution of 20% glycerin and 10% formalin in 0.1M phosphate buffer for 2 days. Then, whole coronal blocks were frozen between glass slides by placing them in -70^{o}C isopentene for 45 min and stored at -70^{o}C.

Patient PN

Case history. PN was a right-handed, Caucasian female born in 1927. She was a lithographer and licensed vocational nurse with at least 11 years of education. She had a history of iron deficiency anemia. PN reported that a car accident in about 1960 resulted in left-sided ambulatory difficulty secondary to a hip fracture. She denied brain injury from this accident. PN had multiple incidents of head trauma not associated with loss of consciousness, though one incident resulted in a left parietal

skull fracture. Her psychiatric history is remarkable for two self-reported suicide attempts.

PN's medical history is also remarkable for heavy alcohol abuse of unknown duration. She continued to binge drink while living in a board-and-care facility during the 1990s. In 1979, PN was diagnosed with significant memory impairment due to mild-to-moderate Korsakoff's syndrome. A CT scan in 1985 demonstrated decreased tissue density in the thalamus and the caudate nucleus, and cortical atrophy as measured by increased fluid in the frontal sulcal and peri-Sylvian areas (Shimamura et al., 1988). An MRI in 1989 (Squire et al., 1990) revealed enlarged lateral ventricles and a marked reduction in the volume of the mammillary nuclei (less than 5% of mean control volume). The temporal lobe, hippocampal formation, and parahippocampal gyrus were of normal size. PN participated in our studies from 1979 to 2000.

In January, 2000, PN was admitted to the hospital after blood was noted in her stool. Endoscopy revealed damage to the lower portion of the stomach resulting from bile gastritis. The lower portion of her stomach was removed, and the remaining portion was connected to the duodenum. PN died in April, 2000, of a vascular disorder of the intestine. She was 72 years old.

Acquisition and preparation of tissue. Approximately 1 hour after death, the carotid arteries were cannulated and the brain was perfused with 4% paraformaldehyde solution for about one hour. The brain was then removed, and a specimen of a right-sided temporal lobe tumor (thought to be a neurofibroma or meningioma) was taken for evaluation. The brain was then suspended in 4%

paraformaldehyde in .01M phosphate buffer for one day. Then, photographs of the whole brain were taken, and the brain was placed in fresh 4% paraformaldehyde in .01M phosphate buffer. On the following day, the brain was cut into approximately 1-cm thick blocks and returned to 4% parafomaldehyde for 48 hr. Then blocks were placed into a cryoproctectant solution of 10% glycerin and 2% DMSO in .01M phosphate buffer for 48 hr. The blocks were then photographed and placed in 20% glycerin and 2% DMSO in .01M phosphate buffer for 48 hrs. They were then frozen between glass slides by placing them in -70^{0}C isopentane for 35 min and stored at -70^{0}C.

Processing of brain tissue. After the brains were frozen, all three were processed in the same way. Whole coronal blocks were sectioned into left and right hemispheres along the midline commissures. The thalamus and medial temporal lobes were separated and processed separately. Continuous 50 μm sections were then cut through each frozen block using one of two freezing microtomes (a MICROM HM440e or a Reichert sliding microtome). Every tenth section was mounted on a gelatin-coated slide and stained with 0.25% thionin. The unmounted sections were stored in a cryoprotectant solution of 30% ethylene glycol and 25% glycerol in .01M phosphate buffer.

Evaluation of brain tissue. Analysis involved qualitative assessment of the medial temporal lobe and diencephalon bilaterally.

D. RESULTS

Neuropsychological data from the patients will be described first, followed by the postmortem neuropathological findings. As mentioned above, all three patients were tested on multiple occasions. NC was tested for 12 years, MG for 7 years, and PN for 21 years. No significant changes in memory or cognitive abilities were noted in any patient during the years they were studied.

Neuropsychological findings

Data for patients NC, MG, and PN will be presented together with comparable data for four patients (H) with histologically confirmed lesions of the hippocampus (RB from Zola-Morgan et al., 1986; GD, LM, and WH from Rempel-Clower et al., 1996). Five patients with alcoholic Korsakoff's syndrome (KOR) will also be presented (for BL and DM, see Delis et al., 1992; for RC, WF, and JW, see Reber & Squire, 1994).

Table 1 shows scores for the full-scale Wechsler Adult Intelligence Scale-Revised (WAIS-R) and the Wechsler Memory Scale-Revised (WMS-R) for patients NC, MG, and PN as well as the H and KOR groups described. NC, MG, and PN had WAIS-R scores in the normal range but were impaired on the WMS-R, especially on the delay memory index.

Anterograde memory. Table 2 shows scores for six measures of anterograde (declarative) memory function. The scores of eight control subjects (mean age = 50.9

Table 1. Characteristics of Amnesic Patients

		WAIS-R	WMS-R				
Patient group	Age	Full-scale	Attention	Verbal	Visual	General	Delay
NC	39	90	62	80	60	69	<50
PN	56	94	81	77	73	67	53
MG	55	111	112.0	85.5	76.0	77.5	56.5
H (4)	53.2	104.2	107.0	84.0	84.0	80.3	54.0
KOR (5)	53.8	97.4	95.6	64.2	78.8	61.6	55.6

WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised. The full-scale WAIS-R and each of the five indices of the WMR-R yield a mean score of 100 in the normal population with a standard deviation of 15. The WMS-R does not provide numerical scores for individuals who score below 50. Therefore, values below 50 were scored as 50 for computing means. Mean scores are also provided for four patients with histologically confirmed damage to the hippocampus (H: GD, WH, and LM from Rempel-Clower et al., 1996; RB from Zola-Morgan et al., 1986) and five patients with Korsakoff's syndrome (KOR). RB was not tested on the WMS-R. Scores for MG on the WMS-R are the average of two tests. The ages are the age at testing.

Table 2. Memory test performance

Patient Group	Diagram recall	Paired associates	Word recall	Word recognition	50 words	50 faces
NC	3	1-0-1	23	71	31	37
PN	2	1-1-1	29	83	29.0	34.5
MG	6	0-0-2	33	71	30	34
H (4)	4.3	0.8-0.5-1.5	42.3	88.0	28.7	28.3
KOR (5)	3.2	0.2-0.0-1.8	28.6	80.2	29.2	29.8
CON (8)	20.6	5.6-7.6-8.8	71.0	97.7	41.1	38.1

The diagram recall score is based on delayed (10-15 min) reproduction of the Rey-Osterrieth figure (Osterrieth, 1944; maximum score: 36). The paired associates score is the number of words recalled on three successive trials (maximum score: 10/trial). The word recall score is the percentage of words recalled out of 15 across five successive study-test trials (Rey, 1964). The word recognition score is the percentage of words identified correctly across five successive study-test trials (yes/no recognition of 15 new words and 15 old words). The score for words and faces is based on a 24 hr recognition test of 50 words or 50 faces (modified from Warrington, 1984; maximum score: 50; chance: 25). Mean scores are also provided for four patients with histologically confirmed hippocampal damage (H), five patients with Korsakoff's syndrome (KOR), and eight controls (CON) from Squire & Shimamura (1986). RB was tested only on the diagram recall test and the paired associates test. Scores for PN on Words and Faces are the average of two tests.

years) are also included (Shimamura & Squire, 1986). Patients NC, MG, and PN were each impaired at learning new material. Figure 1 shows copies and delayed reproductions of the Rey-Osterrieth figure (Osterrieth, 1944) for the patients and a typical control. Although the patients copied the figure accurately, they were unable to reproduce it after a 10-15 minute delay (Figure 1; Table 2 for scores).

Figure 2 shows the performance of the three patients and controls (n=19) on tests of recall and recognition memory for 20-word lists tested after delays of 15 sec, 10 min, 2 hr, or 1 day (Haist et al., 1992). The patients were impaired at both recall (10% vs. 31%, $p<.05$) and recognition memory (66% vs. 91%, $p<.05$).

Retrograde memory. The three patients and controls were asked 92 questions about public events that occurred between 1950 and 1987 (Squire et al., 1989; NC was designated K1 and PN was designated K5). Participants took a recall test (Figure 3A, left) and also a 4-alternative, recognition memory test for the same questions (Figure 3A, right). All three patients were impaired on questions about the most recent time periods (especially on the recall test) but performed as well as controls on questions about more remote time periods. MG became amnesic in 1986 and thus exhibits retrograde amnesia covering 10-15 years. NC and PN were diagnosed in 1979, but the time of onset of their amnesia is uncertain. Accordingly, some of their impairment on these tests must reflect anterograde amnesia, and it is difficult to know how much of the impairment reflects retrograde amnesia.

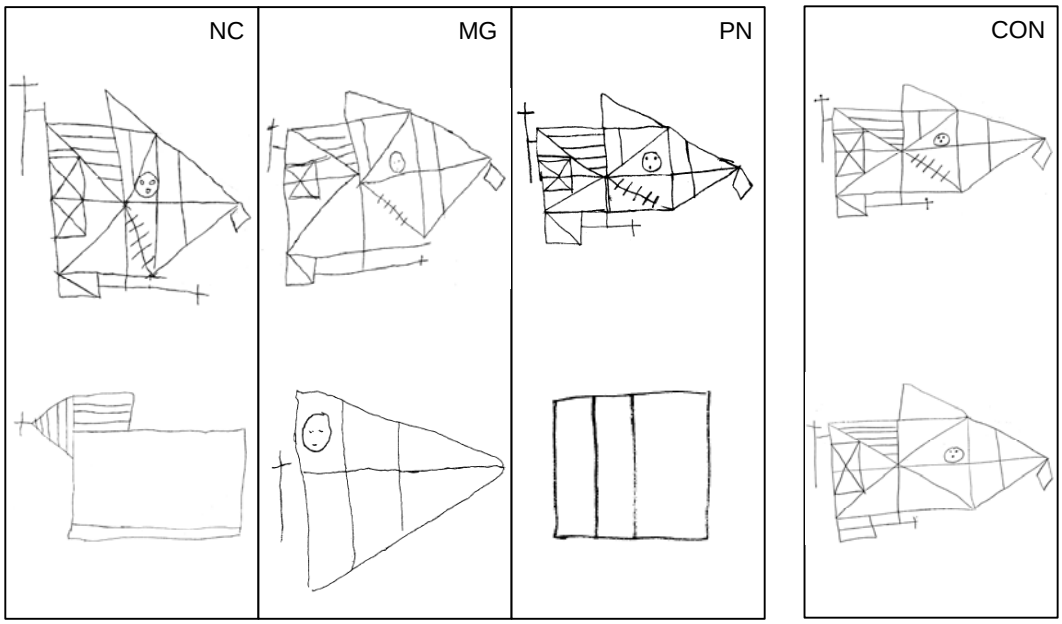

Figure 1. The Rey-Osterrieth figure. Participants copied the Rey-Osterrieth figure (Osterrieth, 1944) and then reproduced the figure from memory 10-15 minutes later, without forewarning. Normal copies (top) and impaired reproductions (bottom) are shown for patients NC, MG, and PN, along with the copy and reproduction of a typical control (CON).

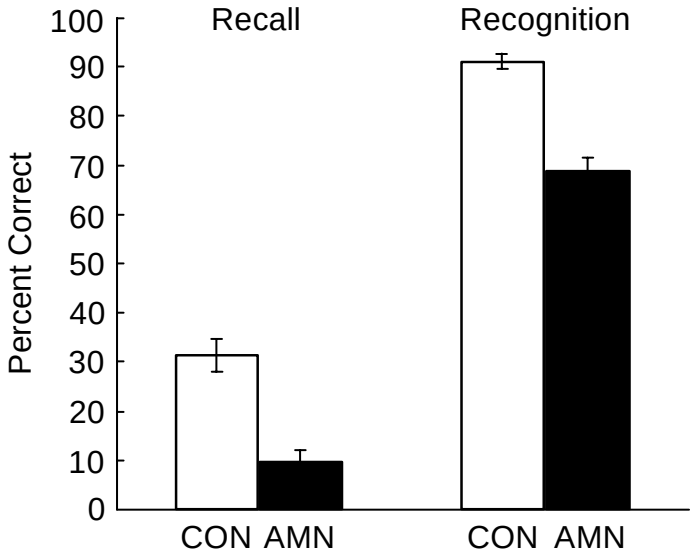

Figure 2. Recall and recognition. The three patients (AMN) and controls (CON, n=19) studied eight lists of 20 words each on eight separate days (Haist et al., 1992). Each participant took four free-recall tests and four 2-alternative, forced-choice recognition tests after delays of 15 seconds, 10 minutes, 2 hours, or 1 day.

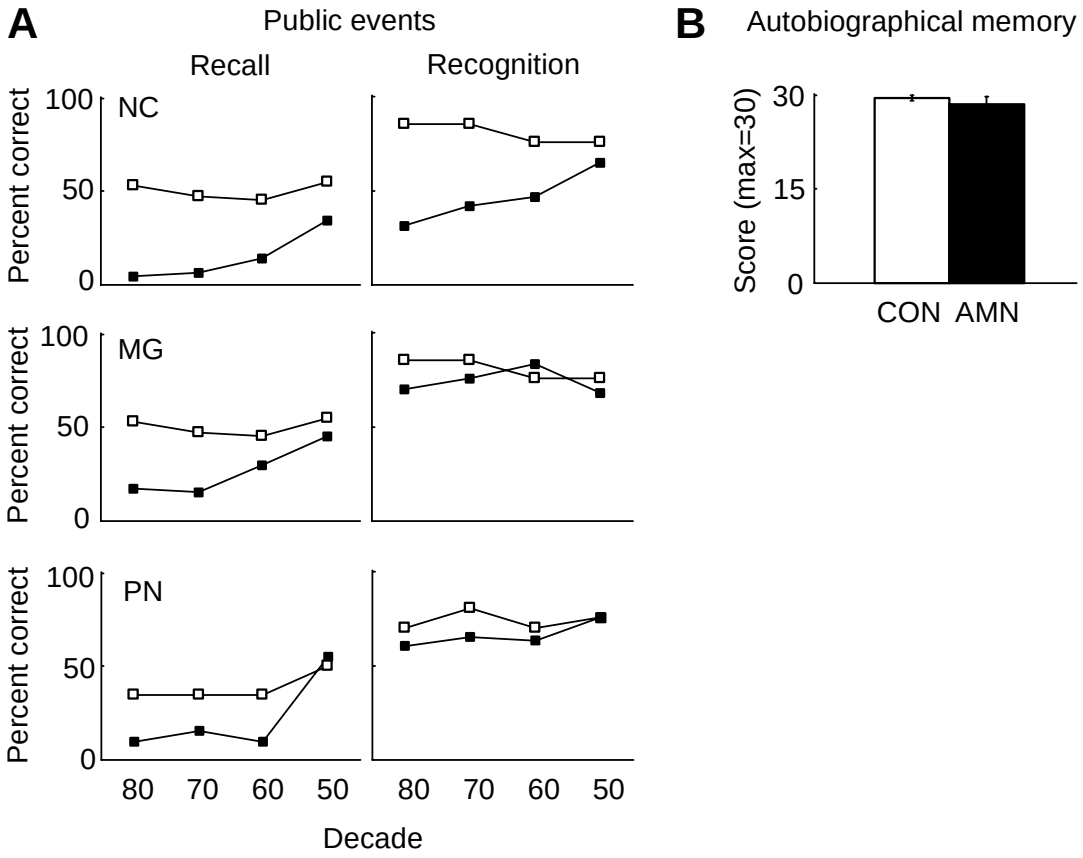

Figure 3. Retrograde memory. (A) Public events. The patients (dark squares) and controls (white squares; n=8 healthy controls for NC and MG; n=9 alcoholic controls for PN) were given recall and 4-alternative recognition memory tests for public events that occurred between 1950-1987. Data from Squire et al. (1989). (B) Autobiographical memory. The three amnesic patients (AMN) and controls (CON, n=5) were given 10 cue words (e.g. nail, book) and asked to recall, in response to each cue word, an autobiographical episode from any past period (Crovitz & Schiffman, 1974). Narratives were rated from 0 (no memory) to 3 (detailed episodic memory specific to time and place). Data for controls from MacKinnon & Squire (1989).

Figure 3B shows performance of the patients and controls (n=5) on a test of autobiographical memory (Crovitz & Shiffman, 1977). Participants were read 10 concrete nouns one at a time and asked to recollect an autobiographical memory associated with each word. Each narrative was rated from 0 (no memory) to 3 (detailed episodic memory specific to time and place). Scores are the sum of the ratings of the 10 narratives (max=30). NC, MG, and PN performed similarly to controls (scores of 28.3 and 29.4, respectively). The amnesic patients (unlike controls) drew a disproportionate number of their autobiographical memories from the very remote past (also see MacKinnon & Squire, 1989).

Nondeclarative memory. Figure 4 shows performance on two tests of nondeclarative memory. For the test of priming, the three patients and controls (n=15) saw 8 words and 8 nonwords one at a time (Haist et al., 1991). After one minute, participants were asked to identify briefly presented words and nonwords (half new and half old). Patients and controls exhibited a similar advantage for identifying old items relative to new items (21.9% and 24%, respectively, for words; 19.0% and 19.9% for nonwords). Thus, the patients exhibited normal priming.

For the test of adaptation effects, the three patients and controls (n=11) lifted 10 identical-appearing objects four times with one hand (Benzing & Squire, 1989). After 20-25 minutes, participants lifted another 10 identical-appearing objects with their other hand once and rated the weight of each object from 1 to 9. Altogether,

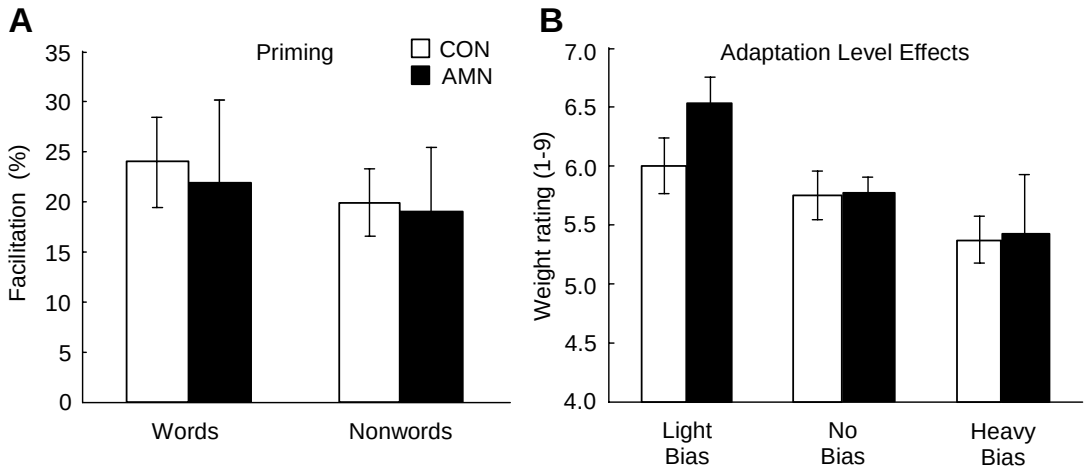

Figure 4. Nondeclarative memory. (A) Priming. The three amnesic patients (AMN) and controls (CON, n=15) saw either 16 words (for an average of 50 msec) or 16 nonwords (for 117 msec), half of which had been presented earlier. The facilitation score is the percentage of previously viewed items that could be correctly identified (i.e., named) minus the percentage of novel items that could be correctly identified. Across four separate study-test sequences, patients and controls exhibited a similar advantage for previously viewed items. From Haist et al. (1991). (B) Adaptation level effects. On three different days, the three patients and controls (n=11) lifted 10 identical-appearing objects that as a group were light, neutral, or heavy. After a delay, participants lifted the 10 neutral objects and rated each object's weight from 1 (extremely light) to 9 (extremely heavy). When participants lifted light objects first, they subsequently perceived the neutral set as heavy (light bias). When participants lifted the heavy objects first, they subsequently perceived the neutral set as light (heavy bias). Patients and controls exhibited these effects to the same degree. From Benzing & Squire (1989).

participants took three different tests in which the first set of objects was lighter than, identical to, or heavier than the second set of objects. Both patients and controls were biased in the same way by their experience with the first set of objects. Thus, the patients exhibited normal adaptation effects.

Performance on other cognitive tests. The memory impairment in NC, MG, and PN appeared largely in the absence of other cognitive deficits. All three scored within normal range on the WAIS-R (Table 1). All three also scored similarly to controls on the Dementia Rating Scale (Mattis, 1976), when the memory subscale was excluded (NC = 110, MG = 119, PN = 112, mean of 11 controls = 115.3; maximum = 119; controls from Janowsky et al., 1989).

The patients also took the Boston Naming Test (Kaplan et al., 1983), the Wisconsin Card Sorting Test (WCST, Heaton, 1981), and the Verbal Fluency Test (Benton and Hamsher, 1976). On the Boston Naming Test, which asks participants to name line drawings of 60 objects, the patients performed similarly to controls (NC = 51, MG = 53, PN = 53, mean of 6 controls = 55.8, range = 49-58; controls from Squire et al., 1990).

On the WCST, which is sensitive to frontal lobe dysfunction, NC, MG and PN sorted 4, 6, and 3 categories respectively (maximum = 6). The Verbal Fluency Test is also sensitive to frontal lobe dysfunction and asks participants to provide as many words as possible in 1 min beginning with the letter F (and then A and S). The patients performed similarly to controls (NC = 31, MG = 32, PN =35, mean of 6 controls = 37.5, range 30-55; controls from Squire et al., 1990).

In summary, all three patients exhibited marked impairment on tests of declarative memory and performed normally on tests of nondeclarative memory and on other tests of cognitive function.

Neuropathological findings

Gross appearance of the brains. All three brains were examined prior to histological analysis. The brain of patient NC appeared normal with no infarcts, atrophy, or sulcal widening. The mammillary nuclei appeared to be normally sized or perhaps slightly reduced in volume. Inspection of blocks of her brain indicated some dilation of the ventricles. Extreme atrophy of the hippocampal formation was also noted bilaterally. MG's brain exhibited marked atrophy and evidence of recent infarcts in the right hemisphere along most of its rostral-caudal extent. The mammillary nuclei were present and of normal size. The brain of patient PN exhibited signs of sulcal widening, especially in the frontal lobes. A small tumor, thought to be a neurofibroma or meningioma, was noted superficial to the right temporal lobe. There was also evidence of a recent, left-sided, occipital infarct. Finally, her mammillary nuclei appeared shrunken.

Patient NC

Medial Temporal Lobe. The primary finding in NC's brain was extensive damage to the entire rostral-caudal extent of the hippocampal formation bilaterally (Figure 5A-D). The CA1 and CA3 fields appear almost completely acellular. The

dentate gyrus is extensively damaged as well, and there appears to be a complete loss of granule cells and hilar cells. The CA2 field and the subiculum appear relatively spared. The perirhinal (Figure 5E) and parahippocampal cortices appear normal. Entorhinal cortex shows some loss of Layer III cells (Figure 5F).

Diencephalon. NC's diencephalon appears normal. The mammillary nuclei are present bilaterally and show no signs of pathology. The mammillothalamic tract and the thalamus bilaterally also appear normal.

Patient MG

Medial Temporal Lobe. MG's medial temporal lobes appear normal, including the hippocampal region, and the entorhinal, perirhinal, and parahippocampal cortices.

Diencephalon. Within the last two weeks of her life, MG suffered a right-sided stroke. The consequences of this stroke were evident throughout the right hemisphere. There was extensive damage in the region of the right thalamus and internal capsule, and we could not distinguish between damage to the right thalamus from the original infarct that caused amnesia and damage from the more recent infarct. Accordingly, analysis of the thalamus was restricted to the left hemisphere.

MG's mammillary nuclei and left mammillothalamic tract appear normal. Figure 6 shows the damage in the left thalamus. Figure 6A shows the most rostral

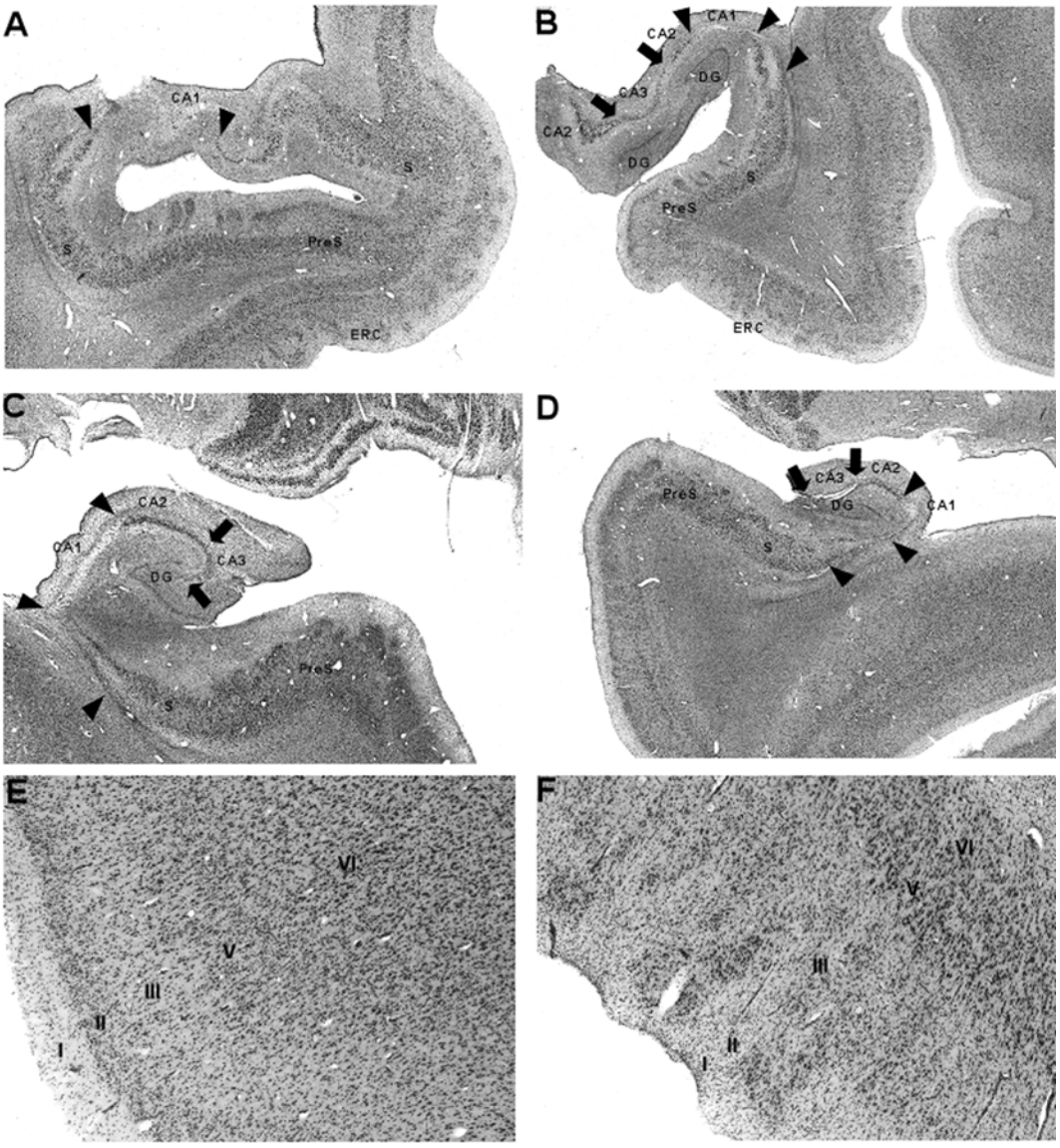

Figure 5. Coronal sections through the left and right hippocampal region of NC rostrally (A,B) and caudally (C,D). The subiculum (S) and presubiculum (PreS) appear normal (A-D). Arrowheads indicate nearly complete cell loss in the CA1 fields bilaterally (A-D). Similarly, arrows indicate nearly complete cell loss in the CA3 fields bilaterally (B-D). The dentate gyrus (DG) also shows nearly complete cell loss bilaterally (B-D). In contrast, CA2 is relatively spared (B-D). Further, the entire hippocampal formation appears reduced in volume, failing to fill the ventricle as expected (C, D). Perirhinal cortex (E) appears normal, but entorhinal cortex (ERC) shows some cell loss in layer III (F). In these two structures, layer IV is absent and is not indicated here.

S = Subiculum. PreS = Presubiculum. DG = Dentate gyrus. ERC = Entorhinal cortex.

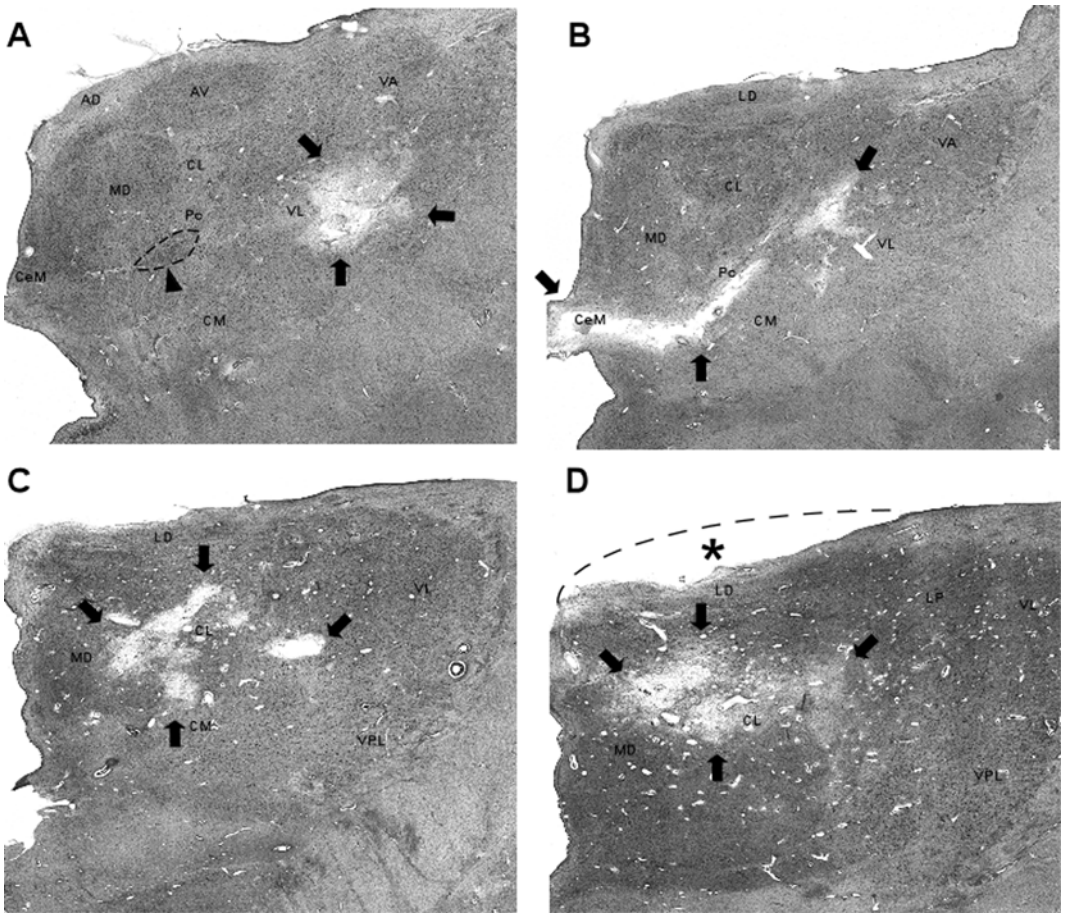

Figure 6. Approximately coronal sections through the left thalamus of MG. At each level, black arrows indicate the lesion. Rostrally (A), the lesion begins in the ventral lateral nuclear complex (likely the motor portion of VLa). At this level, AV and MD appear normal. The arrowhead and dashed oval indicate marked gliosis in the internal medullary lamina (in the region of Pc). 2.5 mm caudally (B), the lesion is still present in the ventral lateral nuclear complex and also includes the internal medullary lamina inferomedially, notably Pc and CeM. Lastly, at 2.5 mm and 5.0 mm caudally (C,D), the lesion damages mainly CL. Also note that the thalamus does not protrude into the adjacent ventricle as expected (the dashed line and asterisk in D indicate the approximate, expected curvature of the superior thalamus). Overall, the rostral-caudal extent of the thalamic lesion is approximately 1-1.5 cm.

AD = Anterodorsal nucleus. AV = Anteroventral nucleus. CeM = Central medial nucleus. CL = Central lateral nucleus. CM = Centre médian nucleus. LD = Lateral dorsal nucleus. LP = Lateral posterior nucleus. MD = Medial dorsal nucleus. Pc = Paracentral nucleus. VA = Ventral anterior nucleus. VL = Ventral lateral nucleus. VPL = Ventral posterior lateral nucleus.

extent of the lesion. In this section, the main damage is in the ventral lateral nucleus (VL, mostly likely the motor portion of VLa), and there is evidence of gliosis medially in the region of the paracentral nucleus (Pc). Figure 6B shows a section 2.5 mm caudally. At this level, the infarct has damaged Pc, the central median nucleus (CeM), and centralis lateralis (CL), which are all considered part of the internal medullary lamina (anterior intralaminar group). CL is also considered part of the mediodorsal nucleus (MD, the densocellular division). Figure 6C and 6D show the lesion caudally 2.5 mm and 5.0 mm, respectively. The focus of the lesion in these sections is CL, with some damage to CM, MD, and VL as well. Finally, note that the overall shape of the thalamus is abnormal, suggesting that the tissue has shifted to fill space left by the lesion (Figure 6D). The other thalamic nuclei, including the anterodorsal nucleus (AD) and anteroventral nucleus (AV), appear relatively normal.

Patient PN

Medial Temporal Lobe. PN exhibits no evidence of pathology in the hippocampus proper, dentate gyrus, or subiculum. The entorhinal, perirhinal, and parahippocampal cortices are normal along their entire rostral-caudal extent.

Diencephalon. PN has extensive damage in the diencephalon. Figure 7 shows damage to the mammillary nuclei bilaterally (Figure 7A-B) and the mammillothalamic tract and AV on the right (Figure 7C-D). There is similar damage in the left mammillothalamic tract and left thalamus. In the mammillary nuclei, gliosis is so pronounced that the few remaining cells are obscured (Figure 7A-B). Figure 7C-D

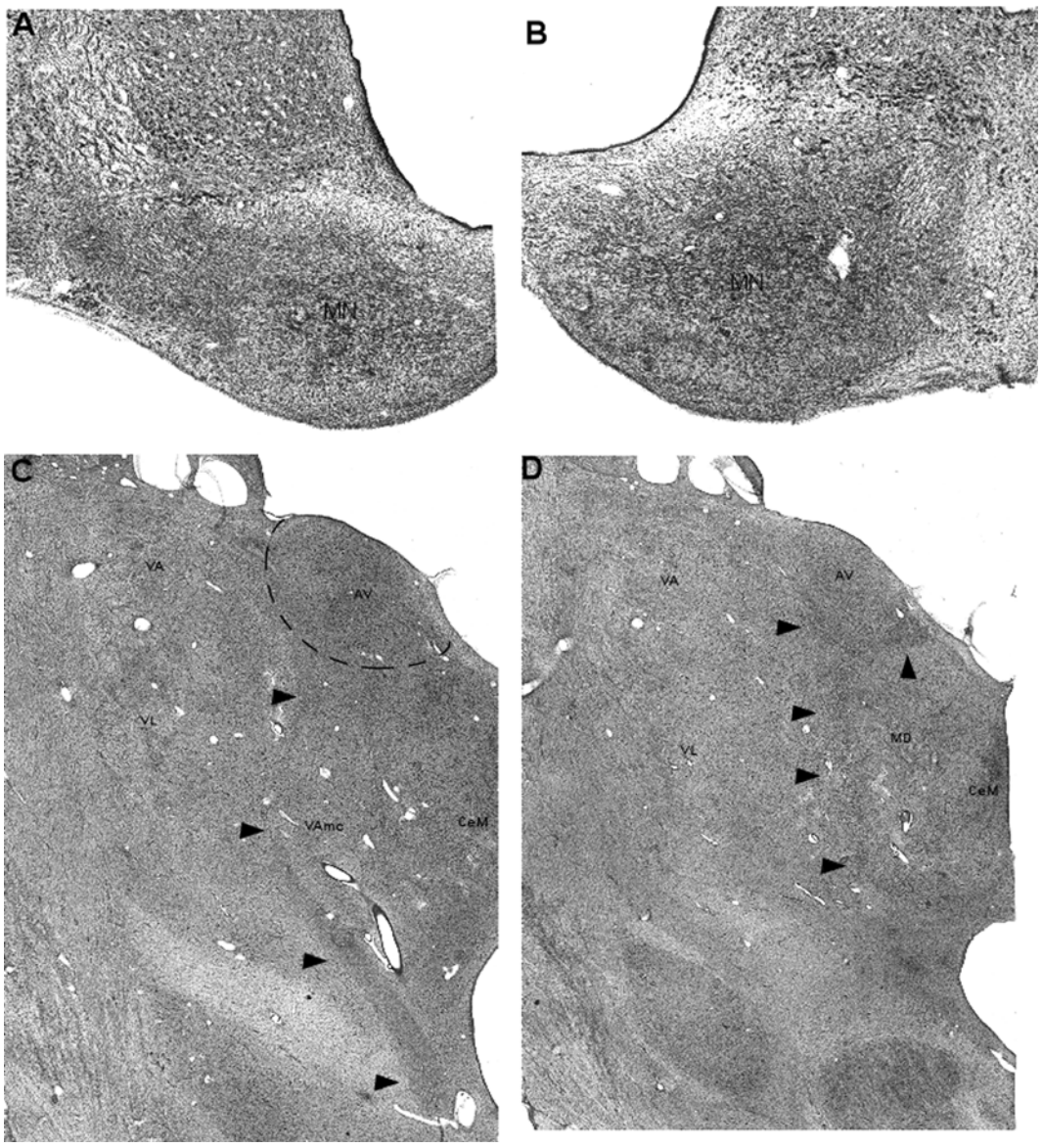

Figure 7. Coronal sections through the diencephalon of PN. The mammillary nuclei (A, right; B, left) show neuronal loss and extensive gliosis bilaterally. In the thalamus, the mammillothalamic tract shows marked gliosis along its course toward the anterior nuclei (arrowheads, C, D). AV also shows neuronal loss and extensive gliosis. The damage is more evident ventromedially than dorsolaterally. AD (which should be evident in both C and D but cannot be detected) is extremely damaged, retaining only a few shrunken cells overwhelmed by glia.

AD = anterodorsal nucleus. AV = Anteroventral nucleus. CeM = Central medial nucleus. MD = Medial dorsal nucleus. MN = Mammillary nucleus. VA = Ventral anterior nucleus. VL = Ventral lateral nucleus.

show that glia have also infiltrated the mammillothalamic tract along its course from the mammillary nuclei to the anterior nuclei (including AV and AD). Within the thalamus itself, AD is damaged so extensively that it is difficult to identify. AV is reduced in volume and neuronal number. Further, AV is extremely gliotic, worse medially than laterally. This pattern of damage is suggestive of primary mammillary nuclei pathology with secondary, transneuronal damage to cells in the anterior nuclei receiving projections via the mammillothalamic tract. The other thalamic nuclei, including MD and CL, appear normal.

Comparison of patients. Figure 8 shows the dentate gyrus and CA3 field (left), the CA2 field (middle), and the CA1 field (right) for each of the three patients. Only NC has damage to the dentate gyrus and the CA3 and CA1 fields. The CA2 field appears relatively normal in all three patients. Figure 9 shows one mammillary nucleus (Figure 9A) and AV (Figure 9B) for each of the three patients. Only PN has damage to both the mammillary nucleus and AV.

E. DISCUSSION

We described neuropsychological and neuropathological findings from three memory-impaired patients (NC, MG, PN). Patient NC had extensive damage to the dentate gyrus, CA1 and CA3 fields of the hippocampus, and some damage to entorhinal cortex in the absence of damage to the mammillary nuclei, mammillothalamic tracts, or thalamus bilaterally. Patient MG had a bi-thalamic stroke

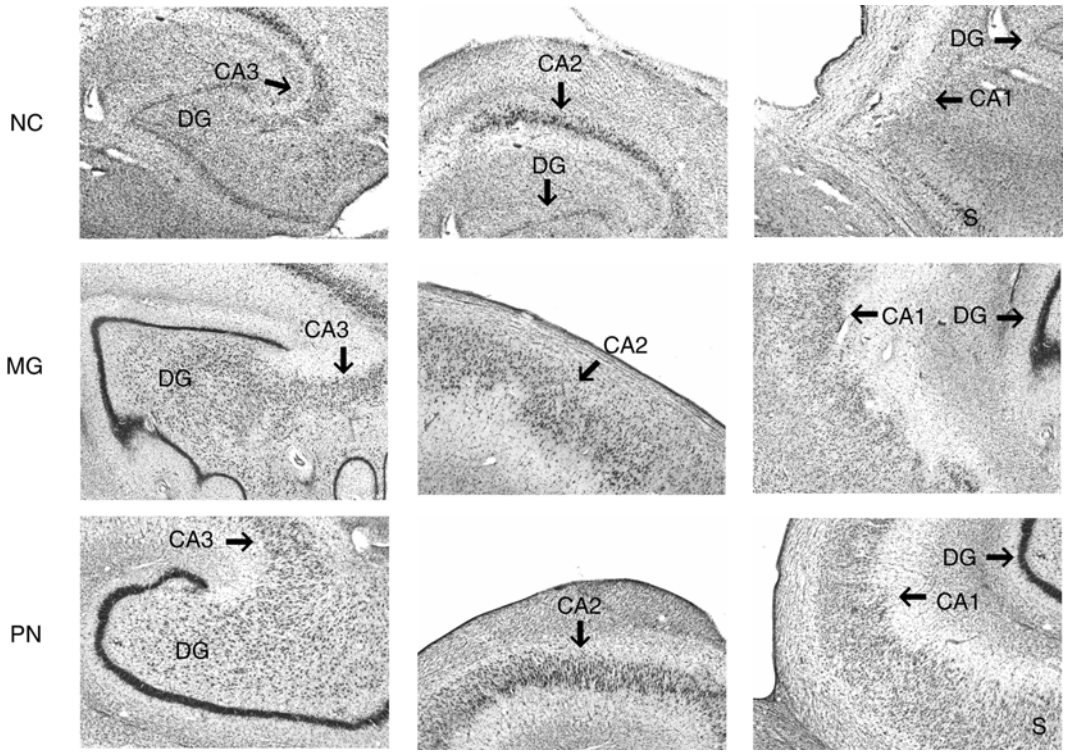

Figure 8. Hippocampal region. Coronal sections through the hippocampal region of each patient. The hippocampal region appears normal in patients MG and PN. In contrast, the hippocampal region of patient NC is markedly abnormal. The dentate gyrus (DG), the CA3 field, and the CA1 field show nearly complete cell loss, although the CA2 field appears relatively normal.

S = Subiculum. DG = Dentate gyrus.

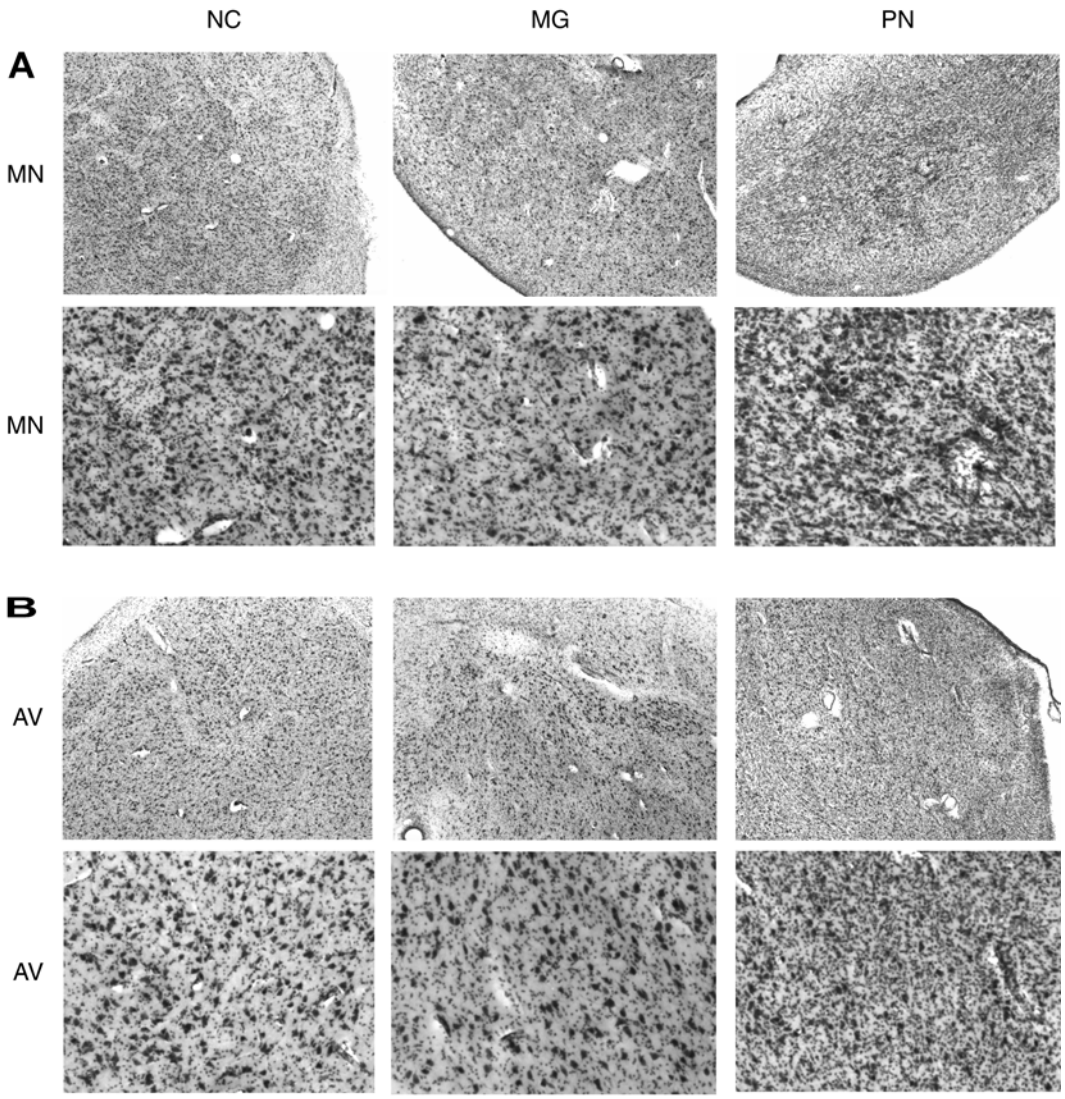

Figure 9. Diencephalon. (A) Coronal sections through one mammillary nucleus (MN) of each patient at low (A, top) and high (A, bottom) magnification. The MN of NC and MG appears normal. In contrast, the MN of PN is gliotic with neuronal loss. (B) Coronal sections through the anteroventral (AV) thalamic nucleus of each patient at low (B, top) and high (B, bottom) magnification. The AV of NC appears normal. The AV of MG appears misshapen but otherwise appears normal (see Results). In contrast, the AV of PN is gliotic with neuronal loss.

MN = Mammillary nucleus. AV = Anteroventral nucleus.

that damaged several thalamic nuclei, including nuclei in the anterior intralaminar group of the internal medullary lamina and MD, in the absence of damage to the mammillary nuclei, mammillothalamic tracts, or medial temporal lobes (MTL). Patient PN had alcoholic Korsakoff's syndrome with damage to the mammillary nuclei, mammillothalamic tracts, and anterior nuclei of the thalamus. All three patients exhibited a common phenotype of amnesia with marked impairment on tests of declarative memory (anterograde and retrograde memory) but normal performance on tests of nondeclarative memory (e.g., priming and adaptation effects) and tests of other cognitive functions (e.g., the WAIS-R and the Dementia Ratings Scale).

Early reports suggested that MTL damage and diencephalic damage produce qualitatively different memory impairments (e.g., Huppert & Piercy, 1979; Parkin, 1984). The consensus now seems to be that damage to either structure produces the same memory impairments (e.g., Weiskrantz, 1985; Victor et al, 1989; McKee & Squire, 1992; Aggleton & Brown, 1999; Van der Werf et al., 2000; Giovanello et al., 2003; Caulo et al., 2005). Our findings strongly support this view. The present study is the first to demonstrate this core amnesic syndrome in a patient with a histologically confirmed lesion to the MTL and patients with histologically confirmed lesions to the diencephalon who all took the same memory tests.

There has been some question about the status of recognition memory in amnesia. One view is that recognition memory is like other declarative memory abilities (e.g., recall memory) and is impaired by damage limited to the hippocampus, extensive damage to the MTL, or damage to diencephalic structures (Haist et al.,

1992; Reed & Squire, 1997; Kopelman & Stanhope, 1998; Kopelman et al., 2001). Several studies have reported that recognition memory is impaired in patients with brain damage limited to the hippocampal region or diencephalon (e.g., Stark et al., 2002; Stark & Squire, 2003; Manns et al., 2003; Zoppelt et al., 2003; Wais et al., 2006; also see single case study RG, Kishiyama et al., 2005). Another view is that recognition memory is normal or near-normal following damage that is limited to the hippocampus or certain diencephalic structures (Aggleton & Shaw, 1996; Aggleton & Brown, 1999). Several studies have reported evidence consistent with this view (e.g., Turriziani et al., 2004; also see single case studies of: patient ROB, Hanley et al., 2001; patient YR, Holdstock et al., 2002; MR, Bastin et al., 2004; KN, Aggleton et al., 2005).

All of the studies mentioned above depend on neuroimaging to determine whether brain structures are damaged. Notably, every study that has characterized brain damage in amnesic patients using post-mortem histology has found impairments in recognition memory. Patient RB, who had damage limited to the CA1 field of the hippocampus, was impaired on tests of two-alternative, forced choice and yes/no recognition memory (Zola-Morgan et al., 1986). Patients GD (damage limited to the CA1 field of the hippocampus), LM (CA1-3, dentate gyrus, entorhinal cortex), and WH (CA1-3, dentate gyrus, entorhinal cortex, subiculum) were impaired on many tests of recognition memory (GD participated in 11 tests, LM in 19 tests, WH in 12 tests, Reed & Squire, 1997; also see Rempel-Clower et al., 1996). Patients EA, BC, JH, and JW (Korsakoff's syndrome including damage to the mammillary nuclei and

midline thalamic nuclei) were also impaired on tests of recognition memory (Mair et al., 1979; Mayes et al., 1988).

In the present study, all three patients were impaired on tests of recognition memory (Table 2, Figure 2). Notably, one study that included all the patients in the present study as well as GD and LM found that recognition memory and recall memory were similarly impaired (Haist et al., 1992). Forgetting curves were constructed for patients and controls who took recall and recognition memory tests for word lists after delays ranging from 15 seconds to 8 weeks. Patients were impaired relative to controls on both tests. Further, when recognition scores were matched by shifting the curve of the patients to overlap the curve of the controls, recall scores were also matched. In addition, the level of impairment on the recognition test predicted the impairment on the recall test in the same way for patients and controls. In summary, overwhelming evidence from amnesic patients with histologically confirmed brain damage suggests that recognition memory is impaired following damage to either the MTL or diencephalon and that recognition memory impairment is similar to the impairment in recall.

In contrast to the debate about recognition memory, there is a consensus that retrograde memory is impaired in patients with MTL or diencephalic lesions (Albert et al., 1979; Mair et al., 1979; Mayes, 1988; Butters & Stuss, 1989; Squire et al., 1989; MacKinnon & Squire, 1989). Despite initial reports that the retrograde memory impairment was the same for recent and remote time periods (Mair et al., 1979), there is now a consensus that retrograde memory impairment is temporally graded (i.e.,

memory for the recent past is impaired more than memory for the remote past) following damage limited to the hippocampal region, extensive MTL damage, or diencephalic damage (Albert et al., 1979; Mayes et al., 1988; Butters & Stuss, 1989; Squire et al., 1989; MacKinnon & Squire, 1989; Squire & Alvarez, 1995; Kapur & Brooks, 1999).

Our results support this view. Confident conclusions about retrograde amnesia can be made for patient MG, the first patient with well-characterized diencephalic amnesia that was not caused by Korsakoff's syndrome to be studied with neuropathology. In patient MG, the retrograde memory impairment was between 10-15 years for semantic knowledge (Figure 3; also see Squire et al., 1989) and perhaps somewhat less for autobiographical knowledge (Figure 3 of MacKinnon & Squire et al, 1989). In summary, the present study confirms that temporally graded, retrograde memory impairment is a common feature of amnesia.

Nondeclarative memory is known to be intact in patients with damage to the MTL (Milner, 1962; Squire & Zola-Morgan, 1988; Squire, 1992; Squire et al., 2004). It is widely accepted that nondeclarative memory is intact in patients with damage to diencephalic structures, although somewhat fewer studies have addressed this issue (as noted by Phaf et al., 2000; Swinnen et al., 2005). Most studies of nondeclarative memory performance in diencephalic amnesia have been primarily studies of patients with Korsakoff's syndrome, and most have concluded that nondeclarative memory is intact (for review, see Butters & Struss, 1989). However, neither neuropathological

study of well-characterized amnesic patients with Korsakoff's syndrome commented on nondeclarative memory (Mair et al., 1979; Mayes et al., 1988).

The present results confirm the view that nondeclarative memory is intact following a lesion to the MTL or diencephalon. In addition to intact priming for words and non-words (Figure 4a) and adaptation effects (Figure 4b), the patients in the present study participated in a number of studies that demonstrated intact nondeclarative memory in patients with amnesia. Intact abilities included: adaptation-level effects (NC, MG, PN, Benzing & Squire, 1989); artificial grammar learning (MG, PN, Knowlton et al., 1992; Knowlton & Squire, 1994; Knowlton & Squire, 1996); category learning (PN, Reed et al., 1999); cognitive skill learning (NC, MG, and PN, Squire & Frambach, 1990); facilitated reading-speed priming (MG, PN, Musen et al., 1990; Musen & Squire, 1991); nonverbal priming for drawings (MG, PN, Musen & Squire, 1992) and pictures (NC, MG, PN, Cave & Squire, 1992); shifts in judgment and preference priming (NC, MG, PN; Squire & McKee, 1992); perceptual identification priming for words and nonwords (NC, MG, PN, Haist et al., 1991; PN, Hamann & Squire, 1997); and probabilistic classification learning (MG, Knowlton et al., 1994; MG, PN, Reber et al., 1996).

The location and extent of brain damage in the patients warrant additional comment. For the 12 years in which NC was studied her memory impairment was thought to be caused by Korsakoff's syndrome due to her long history of alcohol abuse. As noted above, it very difficult to distinguish between amnesia caused by damage to the MTL and damage to the diencephalon based on memory phenotype.

NC received a CT scan as part of a study of diencephalic amnesia, and it is notable that measurements of her brain (unlike the other patients in the study) were within the normal range on almost every measure (Shimamura et al., 1988).

Neuropathological study revealed damage to the CA3 and CA1 fields of the hippocampus, dentate gyrus, and layer III of entorhinal cortex. This pattern of brain damage is unique among the patients with well-characterized amnesia and histologically confirmed lesions of the MTL (Zola-Morgan et al., 1986; Rempel-Clower et al., 1996) and may be related to NC's history of seizures. Evidence suggests that Layer III of entorhinal cortex, which sends projects into the CA1 field of the hippocampus, is epileptigenic and that a prolonged history of seizure can result in Layer III cell loss (e.g., Du et al., 1995). In addition, it has been suggested that the CA2 field is resistant to brain damage induced by seizures (e.g., Amaral & Insausti, 1990). Our findings in NC support these conclusions.

Patient PN had diencephalic damage as a result of alcoholic Korsakoff's syndrome. Brain damage in patient PN is consistent with a recent report that gliosis and neuronal loss in AV (also called the anterior principal nucleus) distinguishes patients with Korsakoff's syndrome from patients with Wernicke's encephalopathy and alcoholic controls (Harding et al., 2000). Similar to other patients with Korsakoff's syndrome, the mammillary nuclei were also extensively damaged in PN (Victor et al., 1989; Mair et al., 1979; Mayes et al., 1988; Harding et al., 2000). Although MD appeared relatively normal in PN, it is possible that gliosis in the mammillothalamic tract (which passes very near MD in its course between the

mammillary nuclei and the anterior nuclei) would have been considered a sign of damage to MD in previous studies.

Finally, the lesion in patient MG included the internal medullary lamina and MD but spared the mammillary nuclei. These results support the view that damage to MD in the absence of damage to the mammillary nuclei can result in memory impairment (Victor et al., 1989; Markowitsch, 1982; Zola-Morgan & Squire, 1985).

It is notable that neither PN nor MG exhibited the paraventricular "band of gliosis" in the region of the paratenial nucleus that was observed in two previous studies (Mair et al., 1979; Mayes et al., 1988). It has been suggested that this band of gliosis could indicate damage to the anterior portion of MD, because the paratenial nucleus (to the extent that it can be identified in the human thalamus) is virtually indistinguishable from MD (Victor et al., 1989; Harding et al., 2000). Further, damage to the paraventricular nuclei is relatively common among patients with Wernicke's encephalopathy in the absence of memory impairment (Victor et al., 1989). Thus, it seems likely that memory impairment in the patients studied by Mair et al. (1979) and Mayes et al. (1988) was not directly related to damage to the paraventricular nuclei.

Taking our findings in PN and MG together with the findings of other patients, it seems likely that there is not a single "critical" lesion that produces diencephalic amnesia. It seems likely that any lesion to the anterior nuclei, mediodorsal nuclei, mammillothalamic tracts, mammillary bodies, internal medullary lamina, and perhaps paraventicular nuclei can cause memory impairment. Involvement of more than one

of these structures seems to increase the likelihood the patient will suffer memory impairment.

In summary, we report that damage to the MTL or diencephalon produces a common amnesic syndrome characterized by impairment in anterograde and retrograde declarative memory (including recognition memory) in the absence of impairment on tests of nondeclarative memory and other cognitive function. Consistent with previous reports, we found that the amnesic syndrome could be caused by damage limited mainly to the hippocampal region (extensively damaging the CA3 and CA1 fields and the dentate gyrus but sparing the CA2 field and subiculum) and Layer III of entorhinal cortex. Also consistent with previous reports, we found that the amnesic syndrome can be caused by damage to structures in the diencephalon that are closely connected to the MTL, including the mammillary nuclei, mammillothalamic tracts, and anterior nuclei of the thalamus. Finally, we report that the amnesic syndrome can be cause by thalamic infarction that spares the mammillary nuclei but damages MD and the internal medullary lamina.

III. QUANTIFYING MEDIAL TEMPORAL LOBE DAMAGE IN MEMORY-IMPAIRED PATIENTS

A. ABSTRACT

Studies of memory-impaired patients will be most useful when quantitative neuroanatomical information is available about the patients being studied. Toward that end, in the case of medial temporal lobe amnesia, protocols have been developed from histological material that identify the boundaries of relevant structures on magnetic resonance images. Because the size of these structures varies considerably in the normal population, some correction for overall brain size is usually employed when calculating volume measurements. Although different correction procedures have been used to normalize for brain size, there has been little study of how well different methods reduce variability and which methods might be most useful. We measured the volume of the hippocampal region (hippocampus proper, dentate gyrus, and subicular complex) and the volumes of the temporopolar, entorhinal, perirhinal, and parahippocampal cortices in five memory-impaired patients and 30 controls. We then compared three different methods for normalizing the volume measurements: normalization by intracranial volume, normalization by aligning the brain to a standard atlas, and normalization by brain area at the level of the anterior commissure. Normalization by intracranial volume reduced variability in the volume measurements of nearly all brain regions to a greater extent than did normalization by other methods. When normalized by intracranial volume, the patients exhibited a mean reduction in

hippocampal volume of about 40% and negligible reductions in the volumes of other medial temporal lobe structures. On the basis of earlier histological analysis of two other patients (L.M. and W.H.), who also had reductions in hippocampal size of about 40%, we suggest that a volume reduction in this range likely indicates a nearly complete loss of hippocampal neurons.

B. INTRODUCTION

Beginning with the earliest case descriptions (Winslow, 1861; Ribot, 1881), the study of memory impairment has provided useful information about the structure and organization of human memory (Scoville & Milner, 1957; Talland, 1965; Baddeley, 1982; Gabrieli, 1998; Squire et al., 2004). In contrast, neuropathological information has only occasionally become available about the patients who have been studied. Yet neuroanatomical information is critical in order to classify patients and to address questions abut how specific brain structures might contribute differently to memory functions (e.g., hippocampus and adjacent medial temporal cortex).

Beginning in the late 1980s, with the development of improved neuroimaging methods, it became possible to relate memory impairment to specific neuropathological change in living patients (Press et al., 1989; Squire et al., 1990; Corkin et al., 1997; Cipolotti et al., 2001; Kopelman et al., 2003; Levy et al., 2003: Vargha-Khadem et al., 2003). These techniques have been especially useful in the case of medial temporal lobe pathology. In most applications, magnetic resonance images (MRIs) are acquired for each patient, anatomic landmarks are identified, and

the volume of each region of interest is measured (for another method based on local gray-matter density, see Ashburner and Friston, 2000). The hippocampus itself is straightforward to identify and measure (Squire et al., 1990), but the adjacent cortical areas do not have readily identifiable borders. However, it has proved possible to establish anatomical landmarks that are visible in MRI, based on histological analysis of healthy brains, and to develop protocols for identifying the temporopolar, entorhinal, perirhinal, and parahippocampal cortices that lie adjacent to the hippocampus (Insausti et al., 1998a; Insausti et al., 1998b, Insausti et al., 2003).

A further difficulty is that measurements of the volume of medial temporal lobe structures can vary substantially among individuals. For example, in one group of 20 healthy controls, the volume of the left temporopolar cortex ranged from 1793 mm^3 to 5016 mm^3 (Insausti et al., 1998a). Such variability makes it difficult to detect small amounts of volume loss in patients.

Following the intuition that variation in the volume of a particular brain structure may be related to variation in brain volume, a common approach to the problem of variability has been to employ some correction for overall brain size. Although a number of different normalization procedures have been employed, there has been little study of how well different methods reduce variability and which methods might be most useful. One study of patients with temporal lobe epilepsy (Free et al., 1995) considered six kinds of corrections and identified three that reduced variability in estimates of hippocampal volume (normalization by cranial area, cranial volume, and intracranial volume). Cranial area refers to the area of the cranial cavity

as measured on a single midsagittal slice. Cranial volume refers to the volume of the cranial cavity plus the temporal bones and the convexity of the skull. Intracranial volume refers to intradural volume.

Similar comparisons have not been carried out in memory-impaired patients, and no studies have been done at all to compare methods for normalizing estimates of volumes of other medial temporal lobe structures. Drawing on MRI data from five memory-impaired patients and 30 controls, we here evaluate three different methods for normalizing volume measurements of medial temporal lobe structures.

C. MATERIALS AND METHODS

Participants

MP-RAGE MR images were collected for 5 memory-impaired patients (4 males and 1 female; Table 3) and 30 matched controls (19 male and 11 female). Three patient scans were done on a 1.5T Siemens magnet at UCSD's Thornton hospital, and 2 were done on a 1.5T G.E. magnet at LDS Hospital in Salt Lake City. Nine control scans (7 male, 2 female) were done on the UCSD scanner, and the remaining scans (12 male, 9 female) were performed on a 1.5T G.E. magnet at the San Diego VA hospital.

Patient J.R.W. became amnesic after an ischemic episode associated with cardiac arrest. G.W. and R.S. became amnesic after respiratory failure associated with drug overdoses. J.S. became amnesic following an episode of carbon monoxide poisoning. L.J. became amnesic during a 6-month period with no known precipitating event. The MRI scans for patients R.S., J.R.W. and J.S. have been reported as part of

Table 3. Characteristics of Amnesic Patients

Patient	Age at scan (years)	Education (years)	WAIS-III IQ	WMS-R Attention	WMS-R Verbal	WMS-R Visual	WMS-R General	WMS-R Delay
JS	36	14	90	92	85	63	81	75
JRW	38	12	90	87	65	95	70	<50
GW	44	12	108	105	67	86	70	<50
RS	45	12	99	99	85	81	82	<50
LJ	66	12	101	105	83	60	69	<50

The Wechsler Adult Intelligence Scale-III (WAIS-III) and the Wechsler Memory Scale-Revised (WMS-R) yield mean scores of 100 in the normal population with a standard deviation of 15. The WMS-R does not provide numerical scores for individuals who score below 50. IQ scores for J.R.W. and R.S. are from the Wechsler Adult Intelligence Scale-Revised. L.J. is female while the other patients are male.

previous studies (Manns et al., 2003), while new scans were obtained for patients G.W. and L.J. (Figure 10). All scans were aligned along the anterior commissure to posterior commissure axis, and voxels were linearly resampled to 1 mm^3 using AFNI (Cox, 1996).

Patient J.R.W. became amnesic after an ischemic episode associated with cardiac arrest. G.W. and R.S. became amnesic after respiratory failure associated with drug overdoses. J.S. became amnesic following an episode of carbon monoxide poisoning. L.J. became amnesic during a 6-month period with no known precipitating event. The MRI scans for patients R.S., J.R.W. and J.S. have been reported as part of previous studies (Manns et al., 2003), while new scans were obtained for patients G.W. and L.J. (Figure 10). All scans were aligned along the anterior commissure to posterior commissure axis, and voxels were linearly resampled to 1 mm^3 using AFNI (Cox, 1996).

Regions of Interest

ROIs for the left and right hippocampal regions (hippocampus proper, dentate gyrus, and subicular complex) were drawn in sagittal view, beginning laterally at the appearance of hippocampal tissue within the lateral ventricle. The drawing continued medially, observing the separation between the hippocampal region and the amygdala. The ROIs were then re-evaluated in coronal view with attention paid to the separation between the hippocampus and the posterior aspect of the pulvinar, the separation between the subicular complex and entorhinal cortex, and white matter/gray matter

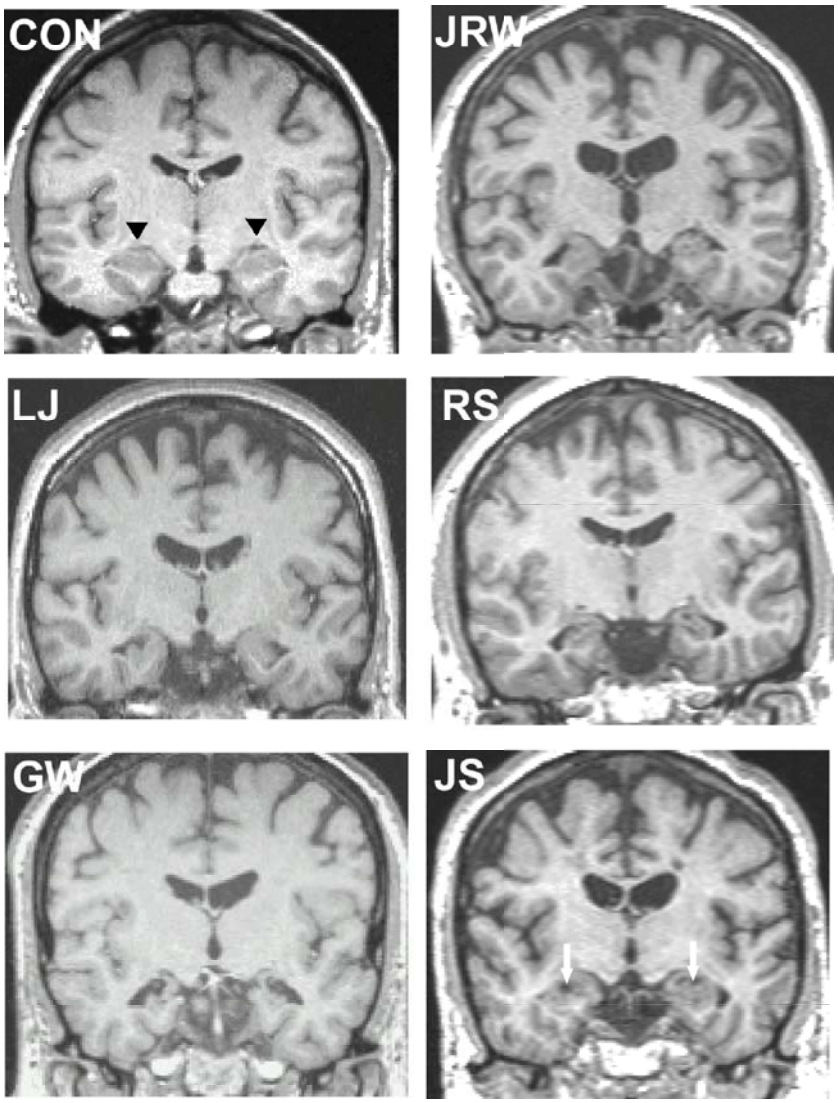

Figure 10. Magnetic resonance images for five amnesic patients and a control (CON). The images are T1-weighted coronal sections through the anterior hippocampus. The black triangles indicate the hippocampal region in the control. The white arrows indicate focal lesions (holes) in the hippocampus of patient J.S.

segmentation.

Segmentation of the parahippocampal gyrus (here including temporopolar, perirhinal, entorhinal, and parahippocampal cortices) proceeded according to the guidelines defined histologically by Insausti et al. (1998a). Parahippocampal cortex was defined rostrally by the coronal section 4 mm posterior to the disappearance of the gyrus intralimbicus (caudal to Insausti slice 24) and caudally by the splenium of the corpus callosum (Insausti et al, 1998b).

These procedures resulted in five ROIs (the hippocampal region and temporopolar, entorhinal, perirhinal, and parahippocampal cortices) for each hemisphere. When brains were analyzed by a second scorer, the volumes for all ROIs were within 10% of the volumes reported here. Next, three different methods were employed to normalize the volumetric data.

Normalization by intracranial volume (ICV)

An ROI was drawn in sagittal view around all brain tissue in every fifth section on average, including ventricular space, and excluding the brainstem below the level of the pons. AFNI then filled in the intermediate sections, and the area within each section was summed to yield the ICV measurement. The raw volumes for each of the five ROIs in each hemisphere were then divided by ICV to obtain the normalized measurement, which is equivalent to expressing each volume as a percent of intracranial volume.

Normalization by area at the anterior commissure (AC)

The AC was identified visually on each scan, and an ROI was drawn around all brain tissue in the coronal section at that level. Raw volumes for each of the five ROIs in each hemisphere were then divided by this area to obtain the normalized measurement, which is equivalent to expressing each volume as a percentage of brain area at the level of the AC.

Normalization by conversion into Talairach space

Standard landmarks were defined manually on the anatomical scans as described by Talairach and Tournoux (1998). The anatomical scans and the raw volumes for each of the five ROIs in each hemisphere were then resampled into Talairach space by AFNI using nearest-neighbor interpolation. The volume of each area after resampling was taken as the normalized measurement.

Comparison of methods for representing volumetric data

We began by calculating coefficients of variation (CoV) for measurements of each of the five ROIs, first when measured as raw volumes and then after each of the three normalization procedures was applied to the data. The CoV is the standard deviation of a sample divided by the sample mean, which is equivalent to expressing standard deviation as a percent of the sample mean. The CoV was used as a measure of variability because it is independent of the magnitude of the measurement. By comparing CoVs, it is possible to assess to what extent the variability in estimates of

regional brain volume can be reduced by applying different corrections (normalization procedures) for differences in overall brain size. A sample that has a smaller coefficient of variation is more homogenous than a sample with a large coefficient of variation. The CoVs were compared using Miller's test for the equivalence of coefficients of variation (Zar, 1991).

D. RESULTS

Volumes in patients vs. volumes in controls

Figures 11 and 12 compare the volumes of the hippocampal region and parahippocampal gyrus in memory-impaired patients and matched controls. Measurements for patients J.R.W., J.S., R.S. and G.W. were compared to the measurements for 19 male controls patients (mean = 49 years old, SEM = 2.37), and measurements for patient L.J. were compared to the measurements for 11 female controls (mean = 67 years old, SEM = 1.03). The male patients as a group showed significant reduction in hippocampal volume ($t[21] = 4.4$, $p < 0.05$) but not in the volume of the parahippocampal gyrus ($t[21] = 1.11$, $p > 0.10$). Patients J.R.W., R.S., and G.W. all had hippocampal volumes more than two standard deviations below the mean of the controls ($z = -4.5$, -3.3, and -4.9, respectively). Patient J.S. had a hippocampal volume within the normal range ($z = .3$), but focal lesions were present (see Figure 10). No male patient had a parahippocampal gyrus volume more than 1.3 standard deviations below the mean control volume. The female patient L.J. also had

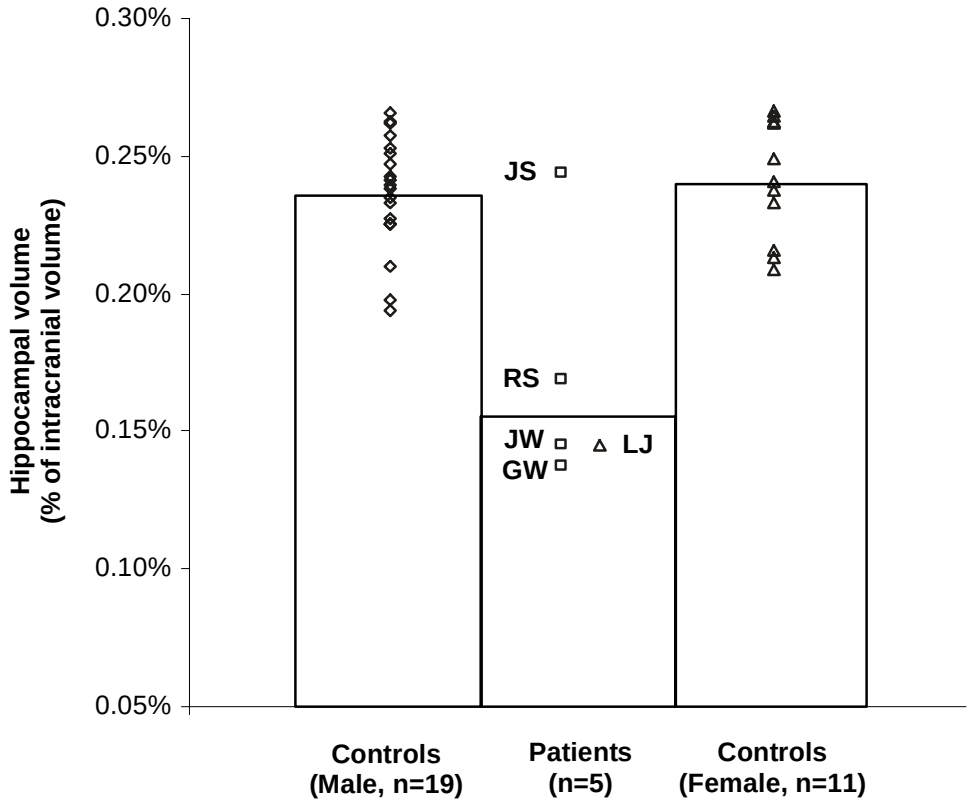

Figure 11. Volume of the hippocampal region for each of 5 patients (4 males, 1 female) and controls (19 males and 11 females). Hippocampal volumes were corrected for differences in brain size by dividing by intracranial volume.

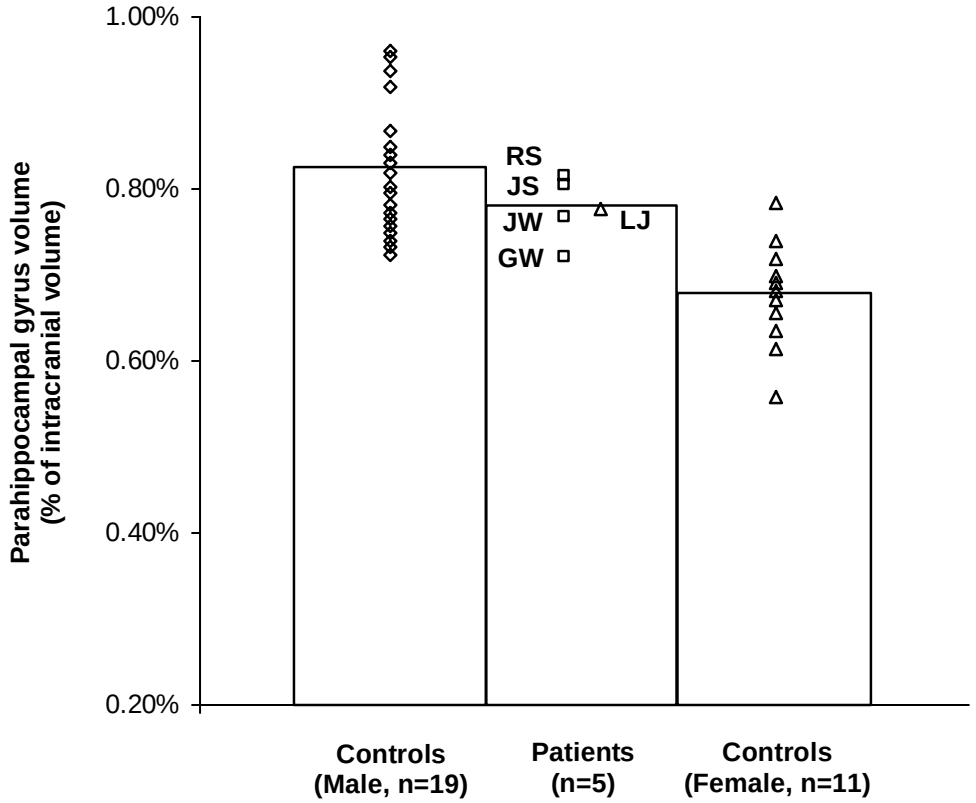

Figure 12. Volume of the parahippocampal gyrus for each of 5 patients (4 males, 1 female) and controls (19 males and 11 females). Parahippocampal volumes were corrected for differences in brain size by dividing by intracranial volume.

a marked reduced hippocampal volume (z = -4.5) and no reduction in the volume of the parahippocampal gyrus (z = 0.8).

Comparison of methods for representing volumetric data

Tables 4 and 5 compare coefficients of variation (CoV) in the male and female control population, respectively, for measurements of the hippocampal region and the cortical regions that lie along the parahippocampal gyrus. Measurements were based on raw (unnormalized) volumes and three different normalization procedures, as described above. The Tables show z scores computed using Miller's test for the equivalence of coefficients of variation, which allows the CoVs of two different samples to be compared. For the Tables, a positive z score indicates that the CoV of the data acquired according to the normalization procedure in the first column is smaller than the CoV of the data acquired according to the normalization procedure in the second column.

Among healthy males (Table 4), the variability of hippocampal volume was significantly smaller for the measurements normalized by intracranial volume than for the raw (unnormalized) measurements of the hippocampal region ($z = 1.99$, $p < .05$). The findings were similar for the parahippocampal gyrus ($z = 2.37$, $p < .05$). The other normalization procedures also reduced the CoV for the hippocampal and parahippocampal gyrus volumes, but the reduction was not significant. Lastly, normalization by intracranial volume reduced variability in nearly all brain regions studied (9 of 10 regions) to a greater extent than did normalization by the other

Table 4. Comparison of methods for representing the volume of medial temporal lobe structures in healthy males

Methods being compared		Hippocampus	Parahippocampal gyrus				
			Total	TPC	PRC	ERC	PHC
1. Normalized by ICV	vs. 4. Raw volume	**1.99**	**2.37**	-0.16	1.06	0.29	1.65
2. Normalized by Talairach	vs. 4. Raw volume	1.86	1.14	-0.38	-0.51	-0.19	1.14
3. Normalized by area at AC	vs. 4. Raw volume	1.59	0.84	0.47	0.42	-0.16	0.66
1. Normalized by ICV	vs. 2. Normalized by Talairach	0.14	1.27	0.22	1.56	0.47	0.53
1. Normalized by ICV	vs. 3. Normalized by area at AC	0.43	1.57	-0.63	0.64	0.45	1.01

The coefficient of variation (CoV) is the standard deviation of a sample divided by its mean. A smaller CoV reflects more homogenous, less variable data. CoVs were calculated from (1) volumes normalized by intracranial volume, whereby each raw volume was divided by intracranial volume; (2) volumes normalized by converting raw volumes into Talairach space; (3) volumes normalized by the area of a single coronal section at the level of the anterior commissure; and (4) raw (unnormalized) volumes. The Table shows Z scores from Miller's test for equivalence of CoVs (Zar, 1991). Positive Z scores indicate that the data in the first column are less variable than the data in the second column. Values in bold indicate a significant reduction in variability for the two methods being compared. In this group of 19 healthy males, the volumetric data were less variable after normalization to intracranial volume than before normalization. Further, the data normalized by intracranial volume were almost always numerically less variable than data obtained by the other methods.

TPC = Temporopolar cortex; PRC = Perirhinal cortex; ERC = Entorhinal cortex; PHC = Parahippocampal cortex; Total = TPC + PRC + ERC + PHC.

Table 5. Comparison of methods for representing the volume of medial temporal lobe structures in healthy females

Methods being compared		Hippocampus	Parahippocampal Gyrus				
			Total	TPC	PRC	ERC	PHC
1. Normalized by ICV	vs. 4. Raw volume	0.48	0.56	-0.39	1.27	0.49	-0.05
2. Normalized by Talairach	vs. 4. Raw volume	-0.19	-0.23	-1.02	0.26	0.15	0.91
3. Normalized by area at AC	vs. 4. Raw volume	0.22	0.45	0.04	0.38	0.37	-0.14
1. Normalized by ICV	vs. 2. Normalized by Talairach	0.67	0.79	0.63	1.02	0.34	-0.96
1. Normalized by ICV	vs. 3. Normalized by area at AC	0.26	0.11	-0.43	0.90	0.12	0.09

The Table shows Z scores from Miller's test for equivalence of coefficients of variation (Zar, 1991). In this group of 11 healthy females, the data normalized by intracranial volume were almost always numerically less variable than the data obtained by other methods.

TPC = Temporopolar cortex; PRC = Perirhinal cortex; ERC = Entorhinal cortex; PHC = Parahippocampal cortex; Total = TPC + PRC + ERC + PHC.

methods, though these differences did not reach significance.

Among healthy females (Table 5), variability was not significantly reduced by any of the normalization methods. Nevertheless, normalization by intracranial volume reduced variability more than the other normalization methods in most brain regions studied (8 of 10 regions).

E. DISCUSSION

We measured the volume of the hippocampus and parahippocampal gyrus bilaterally in five memory-impaired patients and 30 controls. Four of the five patients exhibited significant reduction in hippocampal volume, and none of the patients exhibited significant reduction in the volume of other medial temporal lobe structures. We then compared three different methods for reducing variability in the measurements, all of which involve corrections based on brain size: normalization by intracranial volume, normalization by aligning the brain to the atlas of Talairach & Torneaux (1988), and normalization by brain area at the level of the anterior commissure.

Normalization by intracranial volume (ICV) reduced variability in volume measurements of nearly all brain regions to a greater extent than did normalization by other methods. ICV normalization also has the advantage that it produces an intuitively meaningful number (e.g., the percentage of the total brain volume that is hippocampus). Corrections based on intracranial volume have been used previously when volume measurements are presented, though a standard method for defining ICV

is not in regular use. For example, ICV has been defined as the volume of the supratentorial skull cavity (Kaye et al., 1997) or by an automated segmentation procedure that estimates the volume of white matter, gray matter, and cerebrospinal fluid (Callen et al., 2001). Commonly, a correction based on ICV is used without describing the method (Cipolotti et al., 2001; Mayes et al., 2002). Inasmuch as our method of measuring ICV and the two methods considered by Free et al. (1995) all effectively reduced the variability of volume measurements within the medial temporal lobe, the specific method used to calculate ICV may be less important than insuring that the method is applied identically and reproducibly across brains.

An alternative method for reducing variability is to measure a small area or volume as a proxy for total brain size (Free et al., 1995; Insausti et al, 1998a; Cendes et al., 1993). The area of a coronal section at the level of the anterior commissure is an example of such a proxy measure. This method is attractive because it can be done quickly and is readily explained. However, it has a number of drawbacks. First, abnormally-shaped but normally-sized brains may be incorrectly normalized. Second, because the region used as a proxy is typically small, the size of the region can be influenced by volume loss due to pathology, resulting in inaccurate normalization. Third, while the proxy method does provide a numerical benefit over uncorrected measures of volume, it is not as effective at reducing variaibility as normalization by ICV. Indeed, in agreement with our findings, Insausti et al. (1998a) reported that the proxy method reduced varability in only some regoins of the medial temporal lobe but not in others.

Difficulties can also arise when normalizing volume measurements by aligning brains to a standard atlas (e.g., Talairach space; see Benasconi, et al., 2003 and Pruessner et al., 2002 for recent applications of this method). Our findings suggest that Talairach normalization is useful for normalizing measurements of hippocampal volume but is less useful for other regions of the medial temporal lobe. This method can be viewed as a regional brain size correction. It calculates, for example, the distance between the anterior commissure and the most anterior point of the brain, compares this distance to the standard brain, and then scales the tissue in that region accordingly. Thus, a normal brain with a slightly large frontal lobe and a slightly small occipital lobe will have the anterior portion of the medial temporal lobe (temporopolar cortex) shrunken and the posterior portion (parahippocampal cortex) stretched. Most likely, it is because of this variation in regional brain volume in the normal population that conversion of brains to Talairach space did not provide as great a reduction in variability as ICV normalization.

An additional technique for normalizing volume measurements deserves mention. Pruessner et al. (2002) used the surface area of the collateral sulcus as a basis for normalizing the volumes of medial temporal lobe structures in a large population of healthy individuals. These authors noted, as did Insausti et al. (1998a), that the collateral sulcus presents with a different length, depth, and number of branches in every brain. On the basis of histological observations, Insausti, et al. (1998a) defined the boundaries of medial temporal lobe cortices for all common collateral sulcus lengths, depths, and number of branches. Pruessner et al. (2002)

additionally sought to take into account the variable appearance of the collateral sulcus by measuring its surface area and then dividing the volumes of entorhinal, perirhinal, and parahippocampal cortices by this area.

This method of normalization, while useful for many applications, is less useful for estimating volumes in patients with medial temporal lobe damage. First, corrections based on the collateral sulcus are not useful for patients with damage that includes the sulcus itself. Second, as the authors reported, this normalization procedure improved the variabilty of measurements of perirhinal cortex, but the variability of measurements of entorhinal and parahippocampal cortices increased for 11 of the 12 groups in the study, sometimes by as much as a factor of three (Pruessner et al., 2002; Table 3).

A final observation about the interpretation of hippocampal volume loss is of interest. In the present study, the mean loss of hippocampal volume in the five patients was 33% (if J.S. is excluded because he did not exhibit significant volume loss, the mean was 43%). Cipolotti et al. (2001) described a patient (VC) with approximately 45% loss of hippocampal volume. Isaacs et al. (2003) described six patients with developmental amnesia who had a mean volume loss in the hippocampus of 40%. Lastly, Mayes et al. (2002) described a patient (YR) with a mean volume loss in the hippocampus of 46%. Interestingly, two patients studied previously (L.M. and W.H.) also had an estimated mean reduction in hippocampal size of 41% (based on MRI scans and corrected for temporal lobe size, Squire et al, 1990). On subsequent histological examination (Rempel-Clower et al, 1996), this degree of reduction in

hippocampal size was found to correspond to a loss of nearly all cells in the CA fields of the hippocampus. There was also extensive cell loss in the dentate gyrus, some subicular damage, and some cell loss in entorhinal cortex. These observations suggest that a reduction in hippocampal volume of approximately 40% as estimated from MRI scans likely indicates the nearly complete loss of hippocampal neurons. The tissue collapses with the result that the hippocampus is markedly reduced in volume, but the tissue does not disappear entirely. Thus, a loss of approximately 40% of hippocampal volume as measured from MRI scans should not be taken to mean that 60% of the hippocampus remains functional.

The text of Chapter Three, in full, is a reprint of the material as it appears in

Hippocampus:

Gold JJ, Squire LR (2005) Quantifying medial temporal lobe damage in memory-impaired patients. Hippocampus 15, 79-85.

The dissertation author was the primary researcher and author.

IV. THE HIPPOCAMPUS SUPPORTS BOTH SINGLE-ITEM AND ASSOCIATIVE RECOGNITION MEMORY

A. ABSTRACT

A fundamental issue concerns how the structures of the medial temporal lobe contribute to recognition memory. Some studies suggest that the hippocampus is more involved in memory for associations than in memory for single items. Other evidence suggests that the hippocampus is important for both associative memory and single-item memory and that hippocampal damage similarly impairs both functions. We tested controls and memory-impaired patients with bilateral lesions thought to be limited to the hippocampal region on both a single-item recognition memory test and an associative recognition memory test. In the single-item test, participants studied words and then were tested for their ability to discriminate between study words and novel words. In the associative test, participants studied pairs of words and then were tested for their ability to discriminate between studied pairs and recombined pairs. The patients were impaired on both tests and, like the controls, performed more poorly on the associative test. When the performance of the patients was improved by increasing the number of presentations of the study list (six presentations instead of one), the performance of the patients matched the performance of the controls on both the single-item test and the associative test. These results indicate that the hippocampus similarly supports single-item and associative recognition memory.

B. INTRODUCTION

Declarative memory depends on structures within the medial temporal lobe, including the hippocampal region (subicular complex, CA fields, and dentate gyrus) and the adjacent perirhinal, entorhinal and parahippocampal cortices (Squire et al., 2004; Lavenex & Amaral, 2000; Burwell et al., 1996). A well-studied example of declarative memory is recognition memory, the ability to judge an item as having been encountered previously. A fundamental issue concerns whether specific regions of the medial temporal lobe contribute differently to recognition memory or whether recognition memory depends broadly on the medial temporal lobe.

It has been proposed that recognition memory judgments for items are supported by different neural substrates than recognition memory judgments for associations between items (e.g., Eichenbaum et al., 1994; Henke et al., 1997; Henke et al., 1999; Brown & Aggleton, 2001; Yonelinas, 2002). Several studies have addressed this issue by administering single-item and associative recognition memory tasks to memory-impaired patients (e.g., Kroll et al., 1997; Stark et al., 2002; Stark & Squire, 2003; Giovanello et al., 2003; Mayes et al., 2004; Turraziani et al., 2004).

Some of these studies interpreted their results as suggesting that the hippocampus is more involved in memory for associations than memory for single items (Kroll et al., 1996; Giovanello et al., 2003; Turraziani et al., 2004). These studies involved patients with various amounts of damage to the hippocampal region, adjacent cortex, and other structures, but one objective was to identify the role of the hippocampus in task performance. Other studies, which focused on patients with

damage limited to the hippocampal region, reached a different conclusion. In these studies, patients were similarly impaired at memory for associations and memory for single items (Stark et al., 2002; Stark & Squire, 2003).

In the present study, we administered a memory test similar to the one developed by Giovanello et al. (2003). In the single-item test, patients with damage limited to the hippocampal region studied a list of words and later took a memory test for studied words and novel words. In the associative test, patients studied pairs of words and later took a memory test for studied pairs and rearranged pairs. The patients were impaired on both tests. Finally, the patients were given both tests again but were now provided six exposures to the study material. This procedure improved the performance of the patients to control levels on both the single-item test and the associative test. The results suggest that the hippocampus is similarly important for single-item and associative recognition memory.

C. RESULTS

When each word (or pair of words) on the study list was viewed once, patients (H) were impaired relative to controls (CON) on both the single-item test (37.0 ± 6.8% vs. 65.6 ± 5.0%, $p<.05$) and the paired-items test (21.0 ± 4.5% vs. 48.2 ± 7.9%, $p<.05$) (Figure 13). Repeated measures ANOVA revealed effects of group and test ($p<.05$) but no group x test interaction ($p>.90$). When patients (H 6x) saw each word (or word pair) six times, their scores matched the scores of controls on both the single-item test (61.0 ± 4.1% vs. 65.6 ± 5.0%, $p>.50$) and the paired-items test (38.9 ± 8.0% vs. 48.2 ±

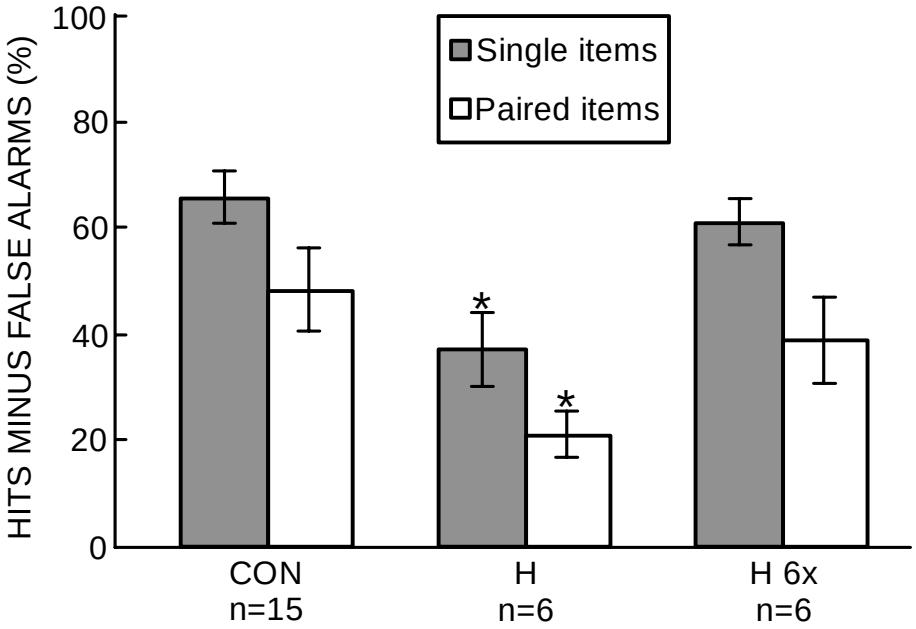

Figure 13. Hit rate minus false alarm rate for controls (CON, n=15) and patients with hippocampal lesions (H, n=6) who studied 36 single items or 18 paired items. In a separate condition (H 6x), the patients with hippocampal damage saw 36 single items six times each or 18 paired items six times each. For the single-item tests, participants took a yes/no recognition memory test for old words and new words. For the paired-items test, participants took a yes/no recognition memory test for old pairs and recombined pairs ($p<.05$). An asterisk indicates a significant difference from CON. Brackets indicate standard error of the mean.

7.9%, p>.50) (Figure 13). Repeated measures ANOVA revealed an effect of test ($p<.05$) but no effect of group ($p>.40$) and no group x test interaction ($p>.70$). Table 6 shows the hit rates and false alarm rates for all three conditions (CON, H, and H 6x).

An analysis of discriminability (d') yielded similar results. Patients (H) were impaired relative to controls (CON) on both the single-item test (1.05 ± 0.21 vs. 2.26 ± 0.21, $p<.05$) and the paired-items test (0.61 ± 0.13 vs. 1.55 ± 0.28, $p<.05$). Repeated measures ANOVA revealed effects of group and test ($p<.05$) but no group x test interaction ($p>.50$). When patients (H 6x) saw each word (or word pair) on the study list six times, their scores matched the scores of controls on both the single-item test (2.01 ± 0.18 vs. 2.26 ± 0.21, $p>.40$) and the paired-items test (1.14 ± 0.22 vs. 1.55 ± 0.28, $p>.40$). Repeated measures ANOVA revealed an effect of test ($p<.05$) but no effect of group ($p>.30$) and no group x test interaction ($p>.70$).

D. DISCUSSION

We investigated the role of the hippocampal region in associative recognition memory and single-item recognition memory. Associative recognition memory was more difficult than single-item recognition memory for both controls and for patients with hippocampal damage. In addition, relative to the controls, patients were impaired on both the single-item test and the paired-items test. In a second condition, the performance of the patients was improved by presenting each study list six times. In this case, the performance of the patients on both the single-item test and the paired-

Table 6. Hit rates and false alarm rates

	Hit rate		False alarm rate	
	Single item	Paired items	Single item	Paired items
CON	75.6 ± 3.8%	74.8 ± 4.7%	10.0 ± 3.3%	26.7 ± 5.1%
H	69.7 ± 3.9%	60.5 ± 8.5%	32.6 ± 8.1%	39.5 ± 6.8%
H 6x	85.9 ± 4.6%	70.3 ± 6.0%	25.0 ± 7.4%	31.4 ± 6.7%

Percent hit rate and false alarm rate (mean ± standard error of the mean) for controls (CON, n=15) and patients with hippocampal lesions (H, n=6) who studied either 36 single items or 18 paired items. In the 6x condition, the same patients with hippocampal damage (H 6x) saw either 36 single items six times each or 18 paired items 6 times each.

items test was similar to the performance of controls who saw each study list only once. Thus, patients with damage limited to the hippocampal region were similarly impaired at both single-item recognition memory and associative recognition memory.

These findings complement earlier studies of memory-impaired patients that used two-component stimuli (e.g., pictures of faces and houses, pictures of two objects, two-syllable words, and two-syllable pseudo-words). In these studies, patients with damage thought to be limited to the hippocampal region were also similarly impaired at memory for associations and memory for single items (Stark & Squire, 2003; Stark et al., 2002).

Other studies of memory-impaired patients have also compared memory for associations and memory for single items (Kroll et al., 1996; Giovanello et al., 2003; Turraziani et al., 2004; Mayes et al., 2004). Patient YR performed similarly to controls on tests of item memory and tests of within-domain associative memory (e.g. word-word pairs or face-face pairs) but was impaired relative to controls on tests of cross-domain associative memory (e.g. word-face pairs) (Mayes et al., 2004). In other studies, patients performed similarly to controls on tests of item memory but were impaired on tests of within-domain associative memory (Kroll et al., 1996; Turraziani et al., 2004) and cross-domain associative memory (Turraziani et al., 2004). Lastly, a different group of memory-impaired patients was impaired at both item memory and within-domain (word-word) associative memory but was more severely impaired on the test of associative memory (Giovanello et al., 2003).

Findings from these studies are at odds with findings from the present study and with each other, perhaps because the location and extent of brain damage, as well as the severity of memory impairment, vary in the patients that have been studied. For example, on the basis of quantitative, volumetric assessment of their lesions, our patients appear to have damage limited to the hippocampal region (Gold and Squire, 2005; Bayley et al., 2005). By contrast, YR is the only patient in the other studies with quantitative evidence of damage limited to the hippocampal region (Mayes et al., 2004). Nonetheless, all the studies under discussion attempted to draw conclusions about the role of the hippocampal region in item memory and associative memory.

Of the previous studies, the present study is most similar to the study by Giovanello et al. (2003). Both studies gave words to memory-impaired patients, and both found that the patients were impaired at single-item memory and associative memory. In contrast to the present study, however, Giovanello et al. (2003) found that patients were more impaired on a test of associative memory than on a test of item memory.

The single-item and paired-items tests in these two studies differed in an important respect. In the present study, patients studied a list of single words and then took a memory test for old words and new words (single-item test). In a separate study/test sequence, patients studied a list of word pairs and then took a memory test for old pairs and recombined pairs (paired-items test). In the study conducted by Giovanello et al. (2003), patients studied a single list of words pairs and then took a

memory test that included both single items (old words or new words) and pairs of items (old pairs and recombined pairs).

To explore this issue further, we tested our patients (n=6) and a group of controls (n=8) using the same procedure as in the study by Giovanello et al. (2003). Under these conditions, our patients performed similarly to controls on the single items but were impaired relative to controls on the item pairs (as in Giovanello et al., 2003). Table 7 shows the hit rates and false alarm rates for patients and controls in both the study by Giovanello et al. (2003) and in our replication. Thus, different results were obtained with a recognition memory test that combined single items and paired items (disproportionately impaired associative memory relative to single-item memory) than were obtained with separate single-item and paired-item tests (similarly impaired associative and item memory).

A suggestion about the origin of these different results comes from examining false alarm rates. When separate single-item and paired-item tests were given, controls and patients had a higher false alarm rate in the paired-items test than in the single-items test (Table 6). This effect is well known when novel items are used as foils in single-item tests and recombined pairs are used as foils in paired-item tests (Table 2 of Stark & Squire, 2003; Kroll et al., 1996; Reinitz et al., 1996). Indeed, both the patients tested by Giovanello et al. (2003) and the patients in our replication of that study exhibited the expected high false alarm rate for recombined pairs (Table 7). In contrast, the controls tested by Giovanello et al. (2003) and the controls in our replication had false-alarm rates for item pairs that were lower than expected and

Table 7. Hit rates and false alarm rates for combined single-item and paired-items test

	Hit rate		False alarm rate	
	Single item	Paired items	Single item	Paired items
CON	74%	82%	10%	12%
H 6x	82%	75%	16%	38%
G.CON	76%	97%	6%	8%
G.MTL 6x	77%	73%	15%	36%

Percent hit rate and false alarm rate (mean) for controls (CON, n=8 from the present study and G.CON, n=11 as reported in Table 2 of Giovanello et al., 2003) and memory-impaired patients (H 6x, n=6 from the present study and G.MTL 6x, n=10 as reported in Table 2 of Giovanello et al., 2003) who studied 36 paired items and took a yes/no recognition memory test for old words, new words, old pairs, and recombined pairs. Patients in both studies saw 36 pairs of items 6 times each.

similar to the false-alarm rates for single items (Table 7). As a result of these low false-alarm rates for recombined pairs, performance of the controls on paired items was actually better than their performance on single items (Table 7). Thus, this unique test procedure (i.e., combining single items and pairs of items into a single test) resulted in low false-alarm rates for recombined pairs and correspondingly good performance for paired items.

In typical recognition memory tasks involving paired items, false alarm rates are high for recombined pairs, presumably because controls and patients base their recognition memory judgments on familiarity, and because recombined pairs are constructed from familiar items. In the unique procedure used by Giovanello et al. (2003) and in our replication, controls may have learned to avoid recognition judgments based on familiarity alone. Such declarative knowledge (i.e., knowledge that judgments based on familiarity are counterproductive) would be difficult for patients to acquire. Alternatively, patients may have had difficulty remembering the complicated task instructions (i.e., respond "old" to single study words and to intact word pairs but respond "new" to single, novel words and to recombined pairs of familiar words). In any case, in the present study when a more straightforward procedure was used (i.e., separate single-item and paired-item tests), the results for control subjects were in line with previous findings from recognition memory studies of single items and paired items. Specifically, the false alarm rate was high for recombined pairs, and paired items were more difficult than single items.

In summary, the present study found that patients with damage limited to the hippocampal region were similarly impaired on a test of single-item memory and a separate test of associative memory. This finding confirms and extends results from previous studies (Stark & Squire, 2003; Stark et al., 2002) and counts against the view that single-item memory and associative memory are distinct functions supported by different structures within the medial temporal lobe. The present results suggest that the hippocampus supports both single-item memory and associative memory. Simple dichotomies do not appear to capture the division of labor of recognition memory function (Squire et al., 2004).

E. MATERIALS AND METHODS

Patients

The memory-impaired patients were five men and one woman with damage thought to be limited to the hippocampal region (dentate gyrus, CA fields, and subiculum) (Table 8). GW and RS became amnesic following a drug overdose and associated respiratory failure in 2001 and 1998, respectively. KE became amnesic in 2004 following an episode of ischemia associated with kidney failure and toxic shock syndrome. JRW and AB became amnesic following an episode of cardiac arrest in 1990 and 1976, respectively. LJ (the female) became amnesic in 1988 during a 6-month period with no known precipitating event.

For 5 of the 6 patients (excluding AB, see below), estimates of medial temporal lobe damage were based on quantitative analysis of magnetic resonance

Table 8. Characteristics of Amnesic Patients

Patient	Age (years)	Education (years)	WAIS-III IQ	WMS-R Attention	Verbal	Visual	General	Delay
AB	69	20	107	87	62	75	54	<50
KE	63	13.5	108	114	64	84	72	55
LJ	67	12	101	105	83	60	69	<50
RS	45	12	99	99	85	81	82	<50
GW	45	12	108	105	67	86	70	<50
JRW	38	12	90	87	65	95	70	<50

Note. The Wechsler Adult Intelligence Scale-III (WAIS-III) and the Wechsler Memory Scale-Revised (WMS-R) yield mean scores of 100 in the normal population with a standard deviation of 15. The WMS-R does not provide numerical scores for individuals who score below 50. IQ scores for J.R.W. and R.S. are from the Wechsler Adult Intelligence Scale-Revised.

images (MRI), compared to data for 19 controls (KE, RS, GW, and JRW) or 11 controls (LJ) (Gold and Squire, 2005). The volumes of the full anterior-posterior length of the hippocampus and the parahippocampal gyrus were measured using criteria based on histological analysis of healthy brains (Amaral and Insausti, 1990; Insausti et al., 1998a; Insausti et al., 1998b). For each patient, the volumes of the hippocampus and parahippocampal gyrus were divided by the intracranial volume to correct for brain size. KE, LJ, RS, GW and JRW have an average bilateral reduction in hippocampal volume of 49%, 46%, 33%, 48%, and 44% respectively (all values more than 3.0 SDs below the control mean). In comparison, the volume of the parahippocampal gyrus (temporopolar cortex, perirhinal, entorhinal, and parahippocampal cortices) is reduced by 17%, -8%, 1%, 12%, and 6%, respectively (all values within 2 SDs of the control mean). On the basis of two patients (LM and WH) with similar bilateral volume loss in the hippocampus for whom detailed post-mortem neurohistological information was obtained (Rempel-Clower et al., 1996), this degree of volume loss likely reflects nearly complete loss of hippocampal neurons (also see Gold and Squire, 2005).

Additional measurements, based on four controls for each patient, were carried out for the insular cortex, fusiform gyrus, frontal lobes, lateral temporal lobes, parietal lobes, and occipital lobes. The only volume reduction in these regions greater than 1.3 SDs of the control mean was the parietal lobe for R.S. (Bayley et al., 2005).

The sixth patient (AB) was unable to participate in MRI studies because he had an implanted pacemaker. His etiology (anoxia) and neurologic examination suggest

hippocampal damage and well-circumscribed amnesia. In addition, high-resolution computed tomography (CT) images obtained in 2001 were consistent with restricted damage to the hippocampal region (Schmolck et al., 2002).

For the six patients, immediate and delayed (12-minute) recall of a short prose passage (Gilbert, Levee & Catalano, 1968) averaged 4.7 and 0.3 segments, respectively.

Controls

The participants in the control group were 15 volunteers (four female) recruited from the San Diego community (age = 58.3 ± 3.1 years, education = 14.3 ± 0.70 years). Their immediate and delayed prose recall averaged 7.7 and 6.7 segments, respectively.

Materials

Materials were drawn from a pool of nouns (40-300 occurrences per million; Kucera and Francis, 1967). For the single-item test, 36 words served as study words. For the test phase, 24 of the 36 study words were selected randomly to serve as targets. Twenty-four additional words served as foils. Target words and foil words were presented in a mixed order such that no more than 3 target words or 3 foil words appeared consecutively.

For the paired-items test, 36 words were used to create 18 study pairs. For the test phase, nine of the 18 study pairs served as target pairs and nine pairs were

recombined to serve as foil pairs. Target pairs and foil pairs were presented in a mixed order such that no more than 3 target pairs or 3 foil pairs appeared consecutively. Study words were equally likely to appear on a single-item test or on a paired-items test.

Procedure

For the single-item test, participants saw 36 words one at a time on a computer screen (self-paced) and were asked to remember each word for a later memory test. Each word was also read aloud to the participants as it appeared on the screen. Words were presented either once (CON and H groups) or six times (H 6x group). After one minute, participants took a yes/no memory test for 24 old words and 24 foil words.

For the paired-items test, participants saw 18 word pairs one at a time on a computer screen (self-paced) and were asked to remember each pair for a later memory test. A sentence that related the two words was read aloud to the participants. After one minute, participants took a yes/no memory test for 9 old pairs and 9 recombined pairs.

Controls (CON) took one single-item test and one paired-items test. The patients with hippocampal lesions (H) took the same tests as controls, plus two additional single-item tests and two additional paired-items tests constructed from new words. The patients also took a different single-item test and paired-items test and received six repetitions of each study list (H 6x). For the H 6x group, study words and study pairs were presented in a different order for each repetition.

For all but two participants, test sessions were scheduled on different days and consisted of one single-item test and one paired-items test (with test order counterbalanced across participants). Patient RS took two of the single-item tests and two of the paired-items tests during a several-hour period on the same day, and patient JRW took three of the single-item tests and three of the paired-item tests during a several-hour period on the same day.

The text of Chapter Four, in full, is a reprint of the material that has been submitted for publication in Learning & Memory:

Gold JJ, Hopkins RO, Squire LR. The hippocampus supports both single-item and associative recognition memory. Under review.

The dissertation author was the primary researcher and author.

V. ITEM MEMORY, SOURCE MEMORY, AND THE MEDIAL TEMPORAL LOBE: CONCORDANT FINDINGS FROM FMRI AND MEMORY-IMPAIRED PATIENTS

A. ABSTRACT

We studied item memory and source memory with fMRI in healthy volunteers and carried out a parallel study in memory-impaired patients. In Experiment 1, volunteers studied a list of words in the scanner and later took an item memory test and a source memory test. Brain activity in the hippocampal region, perirhinal cortex, and parahippocampal cortex was associated with words that would later be remembered (item memory). The activity in these regions that predicted subsequent success at item memory predicted subsequent source memory to a similar degree. In Experiment 2, memory-impaired patients with damage thought to be limited to the hippocampal region were given an item memory test and a source memory test, as in Experiment 1. The patients were similarly impaired on the item memory test and the source memory test. Together, the findings suggest that medial temporal lobe structures broadly support recognition memory function and that item memory and source memory are similarly dependent on these structures.

B. INTRODUCTION

One of the most widely studied examples of declarative memory is recognition memory, the ability to judge an item as having been encountered previously.

Recognition memory depends on the integrity of the medial temporal lobe (MTL), which includes the hippocampal region (subicular complex, CA fields, and dentate gyrus) and the entorhinal, perirhinal, and parahippocampal cortices (Squire et al., 2004). Much of what is known about the anatomy and organization of human recognition memory has come from the systematic study of patients with circumscribed damage to MTL structures. More recently, recognition memory has been studied in the healthy brain using functional magnetic resonance imaging (fMRI).

A useful technique in many of these fMRI studies is the subsequent memory paradigm (Paller & Wagner, 2002). In this paradigm, brain activity is measured with fMRI while volunteers study a list of items (e.g., words or pictures). Later, participants take a recognition memory test outside of the scanner. Brain activity associated with items that will later be remembered can then be compared to brain activity associated with items that will later be forgotten. Typically, structures within the MTL are identified by such a contrast (Henson, 2005).

A fundamental but controversial issue concerns the possible division of labor for recognition memory function within the MTL. Some studies using the subsequent memory paradigm reported that memory for the context in which an item is learned (source memory) is predicted especially by activity during study in the hippocampal region (and possibly parahippocampal cortex) and that memory for the item itself (item memory) is predicted especially by activity during study in the adjacent perirhinal cortex (Davachi et al., 2003; Ranganath et al., 2003). Others have found

that item memory is predicted by widespread activity in the MTL during study, including in the hippocampus (Kirchhoff et al., 2000; Otten et al., 2001; Stark & Okado, 2003). Further, it has been suggested that recognition memory judgments lie along a continuum of memory strength, and that in some respects categories like item memory and source memory can be viewed as representing weaker or stronger memories along the strength continuum (Wixted & Stretch, 2004; Wixted, 2006).

fMRI studies of healthy volunteers and studies of memory-impaired patients provide complementary methods for exploring the anatomy of recognition memory. Yet these two methods have been used infrequently in the same study of memory and cognition. We have carried out an fMRI study of item memory and source memory in healthy volunteers and a parallel study of item memory and source memory in memory-impaired patients.

C. RESULTS

Experiment 1

Behavior

Participants scored 82.5 ± 1.5% correct for the item memory judgment (old/new decision: 76.6 ± 2.6% hit rate and 11.5 ± 1.7% false-alarm rate, d' = 2.03 ± 0.12) and made 82.0 ± 1.5% correct source judgments for the items that they correctly judged as old. The kind of imagery carried out at encoding had no effect on recognition performance (Indoor imagery, 76.9 ± 3.0% correct; Outdoor imagery, 76.2 ± 2.6% correct).

The confidence ratings given during the recognition memory test correlated with successful performance (Figure 14). First, increasing confidence in the item memory decision correlated with item memory success ($r=0.89$, $p<.001$). Specifically, item confidence ratings of 1, 2, and 3 were associated with item memory scores of 54.8%, 69.7%, and 96.9% correct, respectively (Figure 14A). Second, increasing confidence in the source memory judgment correlated with source memory success ($r=0.90$, $p<.001$). Source confidence ratings of 1, 2, and 3 were associated with source memory scores of 56.0%, 74.2%, and 91.2% correct, respectively (Figure 14B). Finally, increasing confidence in the item memory judgments correlated with increasing source memory success ($r=.82$, $p<.001$). Item confidence ratings of 1, 2, and 3 were associated with source memory scores of 56.3%, 69.9%, and 86.8% correct, respectively (Figure 14C).

fMRI results

Four contrasts were of interest: (1) Remembered vs. Forgotten; (2) Item & Source vs. Forgotten; (3) Item Only vs. Forgotten; and (4) Item & Source vs. Item Only. Table 9 shows the regions in the MTL and in other brain areas in which significant activity was identified. The contrast of Remembered vs. Forgotten (Figure 15) identified two regions within the MTL: left hippocampus and a region that included both right amygdala and perirhinal cortex. For both these regions, activity correlated with remembered words was greater than activity correlated with forgotten

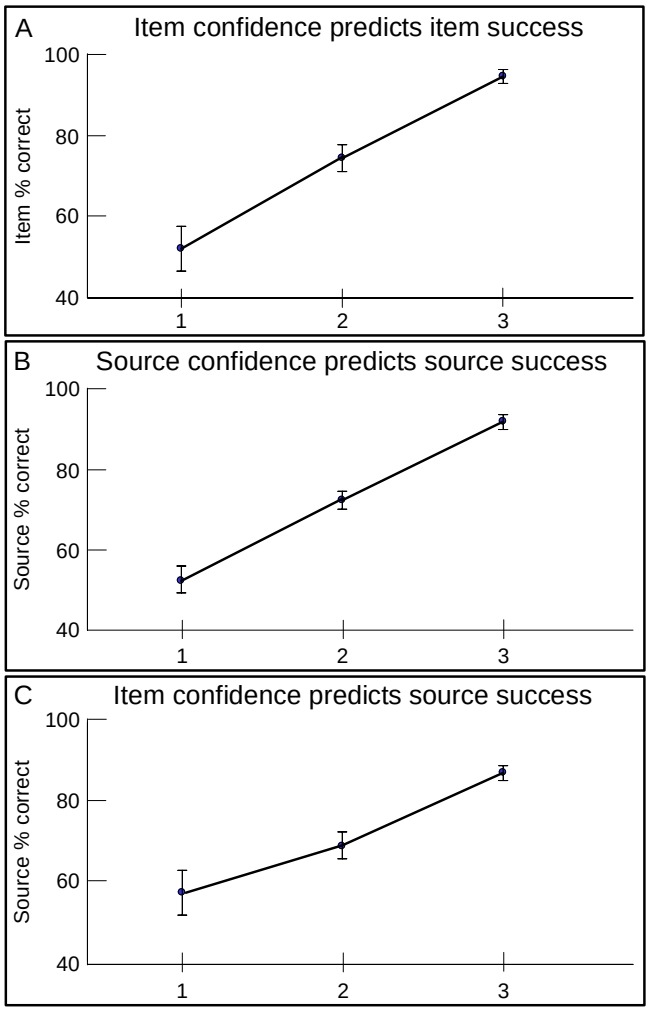

Figure 14. 15 participants rated their confidence in both their item-memory decisions and source-memory decisions. (A) Increasing confidence in the item decision (1, 2, or 3) correlated with increasing item memory success. (B) Increasing confidence in the source decision (1, 2, or 3) correlated with increasing source memory success. (C) Increasing confidence in the item decision (1, 2, or 3) also correlated with increasing source memory success.

Table 9. Brain regions activated during encoding.

Brain Region	Direction of Effect	Area	Talairach Coordinates			Volume (mm^3)
			LR	PA	IS	
Remembered (R) vs. Forgotten (F) (Figure 15)						
Whole Brain (*p*<.05 corrected; minimum cluster size = 391 mm^3)						
Left Lentiform Nucleus	R>F		-22	-1	-4	719
Right Superior Frontal Gyrus	R>F	9	37	44	31	469
Medial Temporal Lobe (*p*<.05 corrected, minimum cluster size = 281 mm^3)						
Left Hippocampus	R>F		-31	-20	-9	562
Right Perirhinal Cortex/Amygdala	R>F	28,34	17	-2	-12	297
Item+Source (IS) vs. Forgotten (F) (Figure 16)						
Whole Brain (*p*<.05 corrected; minimum cluster size = 1078 mm^3)						
Left Inferior Frontal Gyrus	I&S>F	47	-28	30	-4	1547
Right Middle Frontal Gyrus/Anterior Cingulate	I&S>F	11,24	20	41	-8	1422
Medial Temporal Lobe (*p*<.05 corrected, minimum cluster size = 656 mm^3)						
Left Hippocampus	I&S>F		-31	-20	-10	1547
Right Parahippocampal Cortex/Fusiform Gyrus	I&S>F	36,37	-31	-41	-8	891
Right Perirhinal/Amygdala	I&S>F	28,34	29	-40	-12	766
Left Parahippocampal Cortex/Fusiform Gyrus	I&S>F	36,37	16	-2	-11	734
Right Temporopolar Cortex	F>I&S	38	50	17	-14	1000
Item Only (IO) vs. Forgotten (F) (Figure 17)						
Whole Brain (*p*<.05 corrected; minimum cluster size = 391 mm^3)						
Left Insula/Inferior Frontal Gyrus	IO>F	13,47	-38	21	-7	1141
Left Precentral/Middle Frontal Gyri	IO>F	6	-30	-6	50	656
Left Anterior Cingulate/Medial Frontal Gyrus	IO>F	6,9,32	-8	26	35	484
Right Thalamus	IO>F		16	-15	3	422
Medial Temporal Lobe (*p*<.05 corrected, minimum cluster size = 281 mm^3)						
Right Perirhinal Cortex/Amygdala	IO>F	28,34	17	0	-10	328
Left Hippocampus/Perirhinal Cortex/Amygdala	IO>F	28,34	-25	-8	-10	297
Item+Source (IS) vs. Item Only (IO) (Figure 18)						
Whole Brain (*p*<.05 corrected; minimum cluster size = 391 mm^3)						
Right Insula/Superior Parietal Lobule*	I&S>IO	13	28	-39	16	1719
Right Caudate/Anterior Cingulate Gyrus	I&S>IO	24	16	1	26	938
Left Insula	I&S>IO	13	-28	-26	23	938
Left Inferior Parietal Lobule*	I&S>IO		-32	-46	22	422
Right Superior Frontal Gyrus	IO>I&S	9	16	55	29	953
Right Inferior Frontal Gyrus	IO>I&S	13,45	45	17	10	750
Right Medial Frontal Gyrus	IO>I&S	6,8	7	43	39	531
Medial Temporal Lobe (*p*<.05 corrected, minimum cluster size = 281 mm^3)						
Left Entorhinal Cortex	I&S>IO	34	-10	-7	-19	359

Note. LR (Left/Right), PA (Posterior/Anterior), and IS (Inferior/Superior). Talairach coordinates indicate the center of mass of each cluster. *Asterisks indicate that, in addition to the brain regions identified, the activity appears to overlie white matter when superimposed on the anatomical images.

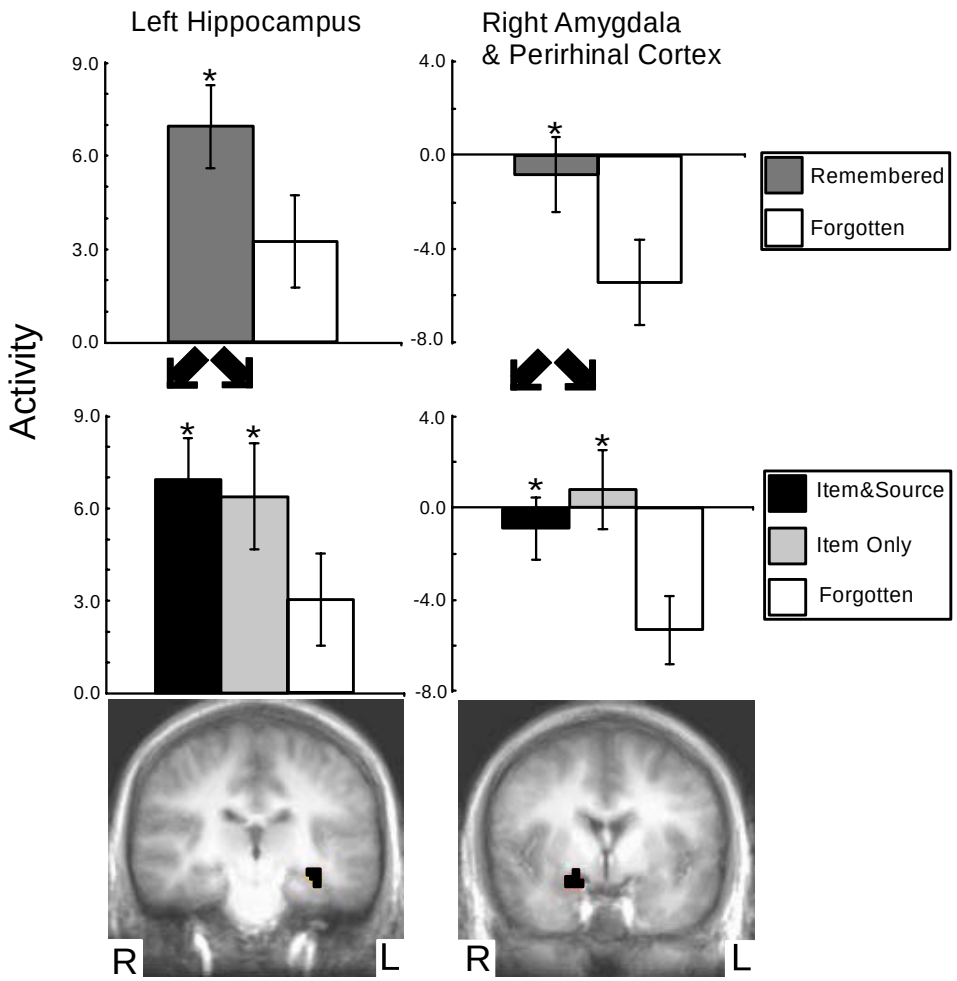

Figure 15. The Remembered vs. Forgotten contrast found two regions in the medial temporal lobe (left hippocampus and right amygdala/perirhinal cortex) that predicted subsequent item memory success, irrespective of source memory success (top and bottom). Within both regions, activity for words that would later be remembered along with correct source memory judgments (Item & Source) was similar to activity for words that would later be remembered but with incorrect source memory judgments (Item Only) (middle). Further, in both regions, there was less activity for words that would later be forgotten (middle). Activity reflects the area under the hemodynamic response function from 0-12 seconds following stimulus presentation. Asterisks indicate a significant difference relative to the Forgotten condition ($p<.05$). Brackets show standard error of the mean. Bottom panel shows center-of-mass of voxel clusters.

words ($p<.05$, top panel). Also, for both regions, activity correlated with Item & Source words was similar to activity correlated with Item Only words ($p>.40$, middle panel). Thus, activity in these regions predicted whether words would be remembered or forgotten but did not predict whether the source judgment would be correct or incorrect.

The contrast of Item & Source vs. Forgotten (Figure 16) identified five regions within the MTL: left hippocampus, a region that included both right amygdala and perirhinal cortex, a region that included both right parahippocampal cortex and fusiform gyrus, a region that included both left parahippocampal cortex and fusiform gyrus, and right temporopolar cortex. For four of the five regions, activity correlated with remembered words was greater than activity correlated with forgotten words ($p<.05$, top panel); in the fifth region (right temporopolar cortex), the activity correlated with remembered words was less than the activity correlated with forgotten words ($p<.05$, top panel). For all five regions, activity correlated with Item & Source words was similar to activity correlated with Item Only words ($p>.45$, middle panel). Thus, activity in all five regions predicted whether words would be Remembered or Forgotten but did not predict whether the source judgment would be correct or incorrect.

Initially, the contrast of Item Only vs. Forgotten did not identify any regions within the MTL. When the contrast included Item Only words that received confidence ratings for the old/new decision of 1 on the 1-to-3 scale (3 words ± 0.8 words per subject), the contrast of Item Only vs. Forgotten (Figure 17) identified two

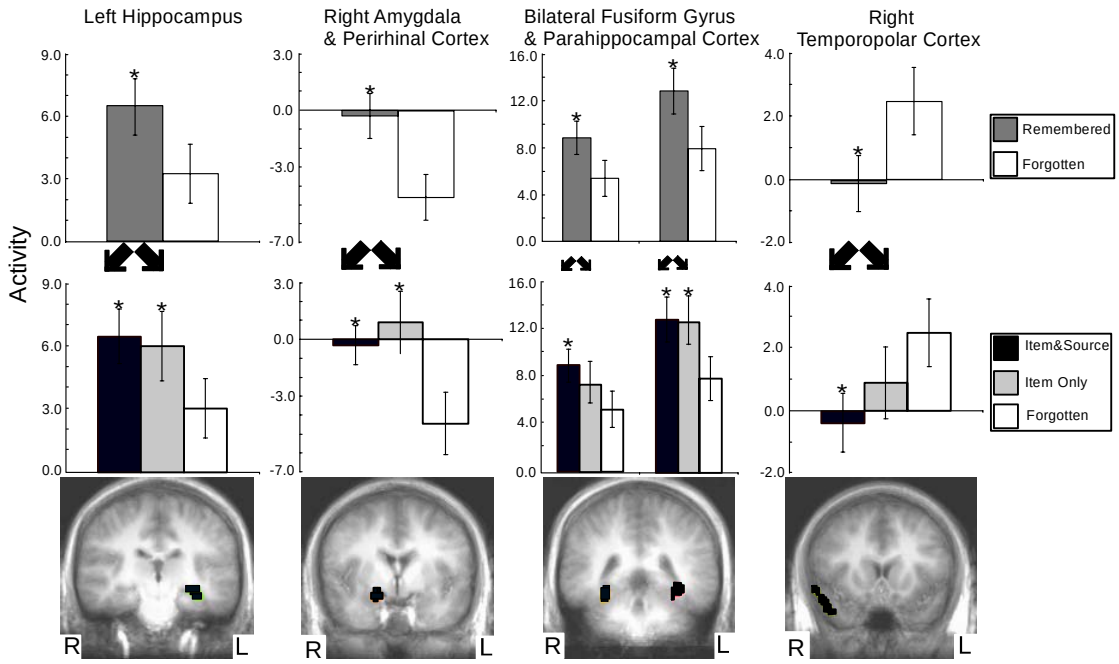

Figure 16. The Item & Source vs. Forgotten contrast found five regions in the medial temporal lobe (the left hippocampus, right amygdala/perirhinal cortex, both the left and right fusiform gyrus/parahippocampal cortex, and right temporopolar cortex) that predicted subsequent item memory and source memory success (middle and bottom). Within all of these regions, activity for words that would later be remembered along with correct source memory judgments (Item & Source) was similar to activity for words that would later be remembered but with incorrect source memory judgments (Item Only) (middle). Activity reflects the area under the hemodynamic response function from 0-12 seconds following stimulus presentation. Asterisks indicate a significant difference relative to the Forgotten condition ($p<.05$). Brackets show standard error of the mean. Bottom panel shows center-of-mass of voxel clusters.

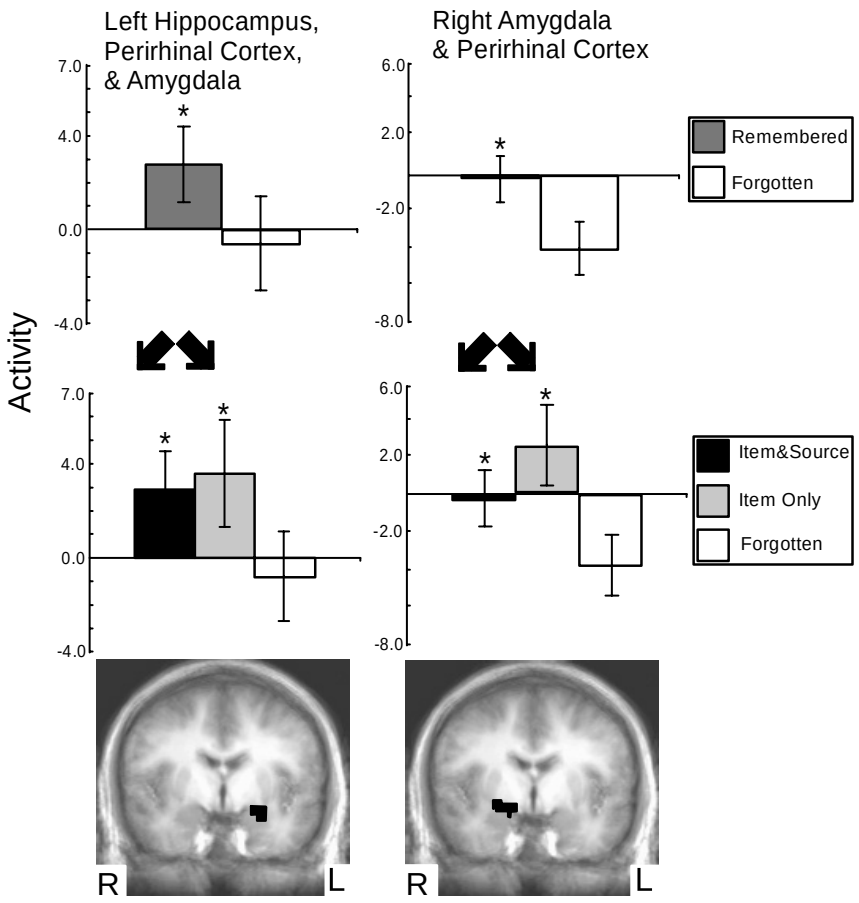

Figure 17. The Item Only vs. Forgotten contrast found two regions in the medial temporal lobe (the left hippocampus/perirhinal cortex/amygdala and right amygdala/perirhinal cortex) that predicted subsequent item memory success along with incorrect source memory judgments (middle and bottom). Within both regions, activity for words that would later be remembered along with correct source judgments (Item & Source) was similar to activity for words that would later be remembered but with incorrect source judgments (Item Only). Further, in both regions, there was less activity for words that would later be forgotten (middle). Activity reflects the area under the hemodynamic response function from 0-12 seconds following stimulus presentation. Asterisks indicate a significant difference relative to the Forgotten condition ($p<.05$). Brackets show standard error of the mean. Bottom panel shows center-of-mass of voxel clusters.

regions within the MTL: one region that included left hippocampus, perirhinal cortex, and amygdala; and a second region that included both right amygdala and perirhinal cortex. For both regions, activity correlated with remembered words was greater than activity correlated with forgotten words ($p<.05$, top panel). For the first region, activity correlated with Item & Source words was similar to activity correlated with Item Only words ($p>.65$, middle panel, left). For the second region, activity correlated with Item Only words was numerically greater than activity correlated with Item & Source words ($p<.07$, middle panel, right).

The contrast of Item & Source vs. Item Only (Figure 18) identified one region within the MTL: left entorhinal cortex. For this region, activity correlated with remembered words was similar to activity correlated with forgotten words ($p>.50$, top panel), but activity correlated with Item & Source words was greater than activity correlated with Item Only words ($p<.05$, middle panel). Thus, activity in this region did not predict whether words would be remembered or forgotten but did predict whether the source judgment would be correct or incorrect.

Experiment 2

Behavior

Figure 19 shows performance for item memory (hit rate minus false alarm rate) and performance for source memory (% correct source judgments for items correctly judged as old). The patients were impaired at item memory relative to controls (CON-1) who took the same memory test (52.0 ± 5.0% for the patients vs. 80.7 ± 5.2% for

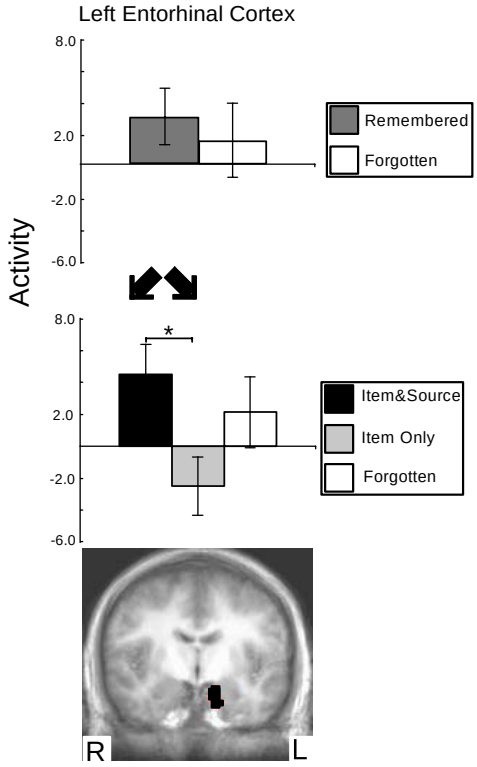

Figure 18. The Item & Source vs. Item Only contrast found one region in the medial temporal lobe (left entorhinal cortex) that predicted item memory success along with correct source memory judgments relative to item memory success but with incorrect source memory judgments (middle and bottom). Within this region, activity for words that would later be remembered along with correct source judgments (Item & Source) was greater than activity for words that would later be remembered but with incorrect source judgments (Item Only). However, in this region activity was similar for remembered words (irrespective of source memory success) and words that would later be forgotten (top). Activity reflects the area under the hemodynamic response function from the 12 seconds following stimulus presentation. Asterisks indicate a significant difference between the activity for Item & Source words relative to Item Only words ($p<.05$). Brackets show standard error of the mean. Bottom panel shows center-of-mass of voxel cluster.

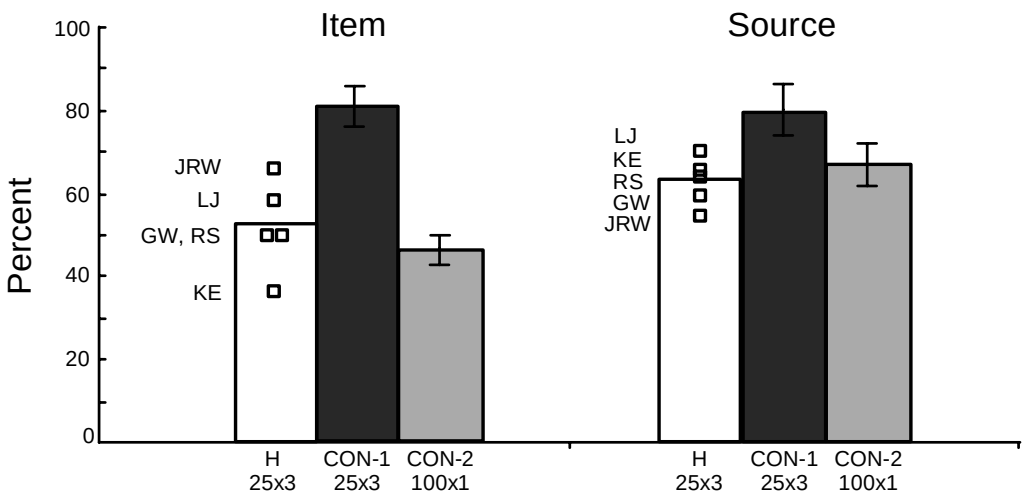

Figure 19. Five memory-impaired patients with damage limited to the hippocampus (H) and six controls (CON-1) learned 25 words by imagining an Indoor or Outdoor scene associated with each word. Each participant saw the 25 words 3 times each (25x3). Patients were impaired relative to controls on both item judgments and source judgments. Six additional controls (CON-2) saw 100 words once each (100x1) and performed similarly to the patients on both item judgments and source judgments. The item score is the Hit rate minus the False Alarm rate (chance = 0%). The source score is the proportion of Hits that were followed by a correct Indoor/Outdoor judgment (chance = 50%).

CON-1, $p<.05$, left panel). Patients scored 76.0 ± 2.6% correct on the item memory judgment (old/new decision: 72.8 ± 5.39% hit rate and 20.8 ± 6.7% false alarm rate, d' = 1.62 ± 0.23), and the CON-1 group scored 90.3 ± 2.6% correct on the item memory judgment (old/new decision: 87.3 ± 2.5% hit rate and 6.7 ± 3.7% false alarm rate, d' = 2.86 ± 0.30). On the source memory test, patients made 62.7% ± 2.5% correct source judgments for the items that they correctly judged as old, and controls made 79.9 ± 5.9% correct source judgments for the items that they correctly judged as old ($p<.05$, right panel). Both source judgment scores were above chance levels (50%, $p<.05$).

Figure 19 also shows that patients performed similarly to controls (CON-2) who studied 100 words a single time, instead of 25 words three times. The patients performed similarly at item memory relative to the CON-2 group (45.5 ± 3.7% for CON-2, $p>.30$, left panel). The CON-2 group scored 72.8 ± 1.8% correct on the item memory judgment (old/new decision: 67.7 ± 6.0% hit rate and 22.2 ± 6.8% false alarm rate, d' = 1.41 ± 0.15). The patients also performed similarly at source memory relative to the CON-2 group (Con-2, 66.5 ± 5.0% correct source judgments for the items that they correctly judged as old, $p>.50$, right panel). Thus, when the controls and patients matched on item memory performance, they also matched on source memory performance.

D. DISCUSSION

Brain activity in 15 healthy volunteers was assessed during the encoding of 175 words. Activity predicting whether or not words would be subsequently

remembered was found throughout the MTL, including the hippocampus, perirhinal cortex, and parahippocampal cortex. Activity in these regions that predicted subsequent success at item memory predicted source memory to the same degree (Experiment 1). In Experiment 2 memory-impaired patients with damage thought to be limited to the hippocampal region studied words and then took a recognition memory test as in Experiment 1. The patients were similarly impaired at item memory and source memory.

Henson (2005) surveyed 23 studies that used the subsequent memory paradigm that we used in Experiment 1. Most of the studies found activity within the MTL that predicted subsequent success at remembering studied items, though which areas were active varied across studies. Our findings accord with this literature in that we also found activity predicting subsequent item recognition in three different MTL regions: hippocampus, perirhinal cortex, and parahippocampal cortex. Notably, activity in the hippocampus at encoding has often been found to predict subsequent performance on relatively difficult memory tests, such as tests of source memory or tests of associative information (e.g., Davachi et al., 2003; Ranganath et al., 2003; Sperling el al., 2003; Jackson & Schacter, 2004; Kirwan & Stark, 2004). Here, as in other studies that focused on item memory (Kirchhoff et al., 2000; Otten et al., 2001; Reber et al., 2002; Morcom et al., 2003; Stark & Okado, 2003), we found that hippocampal activity predicted subsequent success on a simple test of item memory.

The present findings for perirhinal cortex also accord with findings from earlier fMRI studies of recognition memory and source memory (Davachi et al., 2003;

Ranganath et al., 2003). These two studies, like our study, found that activity in perirhinal cortex at encoding predicted whether or not a word would be subsequently remembered, and further that activity in perirhinal cortex did not predict whether or not correct item memory judgments would be accompanied by correct source memory judgments. However, our finding that MTL activity did not differentially predict correct source memory judgments (with the exception of left entorhinal cortex) contrasts with the findings from these same two studies. These studies found that activity at encoding differed in both the hippocampus and parahippocampal cortex, depending on whether or not source memory was subsequently available (Davachi et al., 2003; Ranganath et al., 2003).

The source question in these studies involved a relatively salient aspect of the encoding condition (e.g., imagine a scene associated with the word ("Image") vs. read the word backwards ("Read") in Davachi et al., 2003). In comparison, the source question in the present study involved a potentially more difficult judgment (Indoor image vs. Outdoor image). Accordingly, one can ask whether participants in the present study might in fact have had available a significant amount of source memory, even for Item Only words, and lacked only the specific information (Indoor image vs. Outdoor image) that was the basis for the source memory question. If so, it might not be surprising that activity in MTL structures did not differ in the case of remembered words that were also assigned the correct source (Item & Source) and remembered words that were assigned the incorrect source (Item Only).

One way to view studies of recognition memory (with respect to activity in the MTL) is to suppose that item information and source information vary in memory strength and that items for which source information is available are remembered with greater memory strength than items for which less source information is available (Wixted & Stretch, 2004; Wixted, 2006; also see Cansino et al., 2002). Indeed, our Figure 2 shows that words for which participants have stronger memory are also words for which they are likely to make correct source judgments. This finding has also been reported for other item memory tasks and source memory tasks (Slotnick et al., 2000; Slotnick et al., 2005). Accordingly, while the present study treated item memory and source memory as dichotomous categories, the results we obtained can be understood as reflecting differences in memory strength. Thus, the confidence ratings associated with forgotten words, Item Only words, and Item & Source words were 2.04 ± .09, 2.47 ± .07, and 2.76 ± .04, respectively. Notably, the difference between the confidence ratings associated with Item Only words and forgotten words was marginally greater than the difference between Item & Source words and Item Only words (0.43 ± .06 vs. 0.30 ± .04, $p<.08$). Perhaps this observation can account for why hippocampal activity at encoding predicted subsequent success at recognizing items but did not differentially predict success at making source judgments.

Neither Davachi et al. (2003) nor Ranganath et al. (2003) reported average confidence ratings for remembered words, forgotten words, Item & Source words, or Item Only words. If the difference in memory strength between remembered words (or Item Only words) and forgotten words in those studies was small, such a result

could explain why hippocampal activity did not predict subsequent item memory. Similarly, if the difference in memory strength in those studies between Item & Source words and Item Only words was great, such a result could explain why hippocampal activity in these studies did predict subsequent source memory success. Studies that manipulate the strength of item memory and source memory could provide a test of these possibilities.

The results from Experiment 2 are consistent with the findings from Experiment 1 and count against the view that the hippocampal region is especially important for source memory. Patients with damage to the hippocampal region were impaired on both the item memory test and the source memory test. Further, when patients and controls were equated for item memory performance by having controls study more words fewer times each, the two groups performed similarly to controls on both the item memory test and the source memory test. This finding suggests that the hippocampus supports item memory and source memory judgments to a similar degree. Accordingly, Experiment 2 provides no basis for supposing that the hippocampus is especially important for source memory. Note, however, that the present findings are not an argument against the utility of the distinction between item and source memory itself (or the related concepts of recollection vs. familiarity and remembering vs. knowing) (Wais et al., 2006; Wixted, in press). For example, source memory may depend especially on the strategic, effortful search that is the province of the frontal lobes (Buckner & Wheeler, 2001).

In an important study (Glisky et al, 1995), elderly participants were divided into groups (high or low MTL function and high or low frontal lobe function) based on their performance on standard neuropsychological tests. High MTL function was related to good performance on an independent test of item memory, while high frontal lobe function was related to good performance on an independent test of source memory. This finding suggests that memory for items depends on the MTL, while memory for sources depends importantly on the frontal lobe. Subsequent work by the same group (Glisky et al, 2001) tried to rule out the possibility that individuals with low frontal lobe function are impaired at source memory tests simply because source memory judgments are more difficult than item memory judgments. Item memory was assessed using a more difficult test than previously, yielding a score of about 70% correct instead of about 85% correct. (The source memory score was about 60% correct.) Despite the greater difficulty of the item memory test, participants with low frontal lobe function still performed well on the item memory test but poorly on the source memory test.

In a different study, patients with frontal lobe damage performed at normal levels on a test of item memory (recall of recently learned, obscure facts) but were impaired at source memory (recall and recognition of the context in which the facts were learned) (Janowsky et al., 1989). In another study, frontal lobe patients performed similarly to controls on item memory (sentences and words) but were impaired relative to controls on source memory tests (Johnson et al., 1997).

The present results are consistent with these earlier findings. In Experiment 1, the hippocampus was identified by the Remembered vs. Forgotten contrast (item memory) but not by the Item & Source vs. Item Only contrast (source memory). However, the Item & Source vs. Item Only contrast identified three brain regions in the right frontal lobe (Table 9). Activity in these three frontal regions was greater for Item Only words than for Item & Source words. Participants may have expended more effort when it was difficult to create a mental image than when a mental image came easily to mind. (In the former case, the image would not be expected to be remembered as well as in the latter case.) Further work with fMRI investigating the role of the frontal lobes in source memory is warranted.

In summary, with the exception of a region of left entorhinal cortex, activity within the MTL predicted which items would be subsequently remembered but did not differentially predict which items would later be accompanied by accurate source judgments (Experiment 1). In addition, patients with hippocampal damage were similarly impaired on item memory and source memory tasks (Experiment 2). Note that the present findings are not an argument for the view that the structures of the MTL carry out one undifferentiated function. But the findings do caution against the simple idea that processes like item memory and source memory can be neatly dichotomized and assigned to separate MTL structures.

E. MATERIALS AND METHODS

Experiment 1: fMRI

Participants

The participants were 8 males and 7 females (mean age = 25.3 ± 1.0 years) recruited from the University community.

Stimuli

Stimuli were adjectives with a mean frequency of 55 (range 10-500; Kucera and Francis, 1967). Four lists of 175 words were constructed, two study lists and two foil lists. Eight participants saw one study list (in one of two possible orders), and the 7 other participants saw the other study list (also in one of two possible orders). The yes-no recognition test consisted of the 175 study words and 175 foils presented in a mixed order such that no more than 3 studied words or 3 foils appeared consecutively.

fMRI test procedure

Before entering the scanner, participants were given 3 practice trials with the behavioral task (Figure 20). For the task, participants saw a cue (Indoor/Outdoor) for one second, followed by a study word (e.g., Happy) for one second. Participants were instructed to form a mental image of an Indoor or Outdoor scene (depending on the cue) that was associated with the study word. Across participants, each of the 175 study words was equally likely to be presented with Indoor or Outdoor imagery instructions. Participants were asked to remember the study words for a subsequent memory test, but were not asked to remember the image they formed. A black fixation cross then appeared for four seconds, during which participants formed their

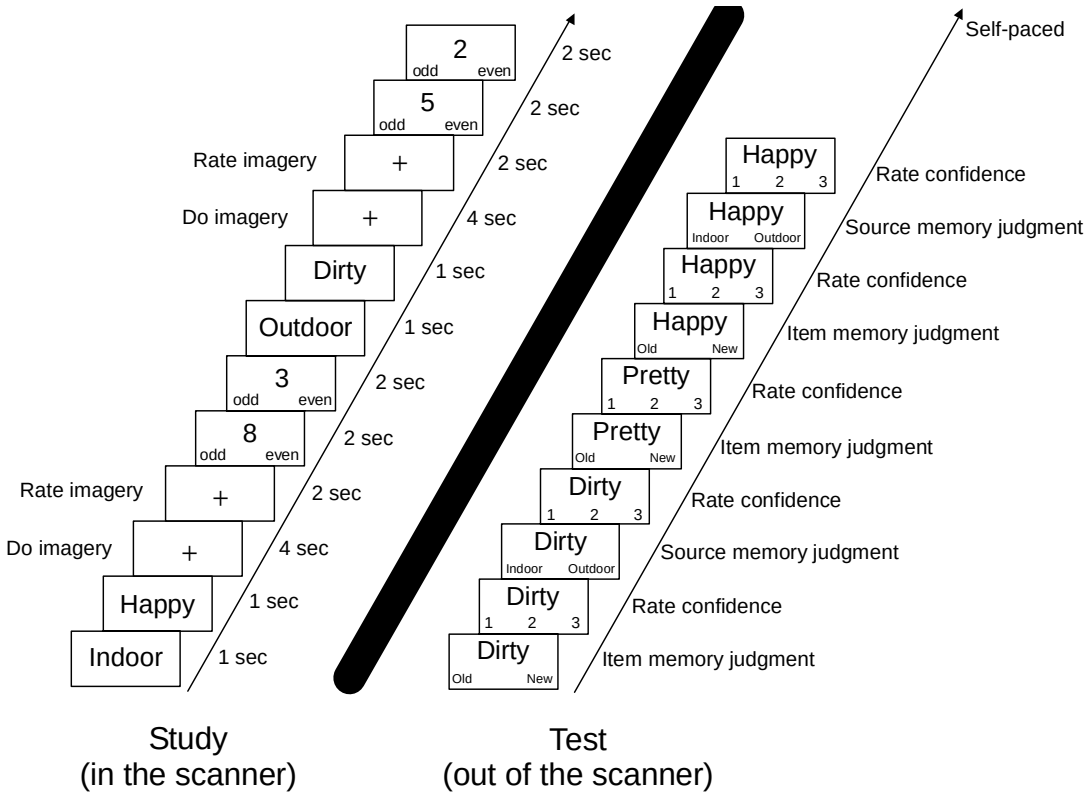

Figure 20. Inside an fMRI scanner, participants learned 175 words (25 words across 7 runs) by imagining an Indoor or Outdoor scene associated with that word. At study, participants were shown a cue (Indoor/Outdoor) for one second, the study word for one second, and then had four seconds to form an indoor or outdoor image as they viewed a fixation cross. After four seconds the cross turned red, instructing participants to rate their success at forming an image on a 0-3 scale. Trials were separated by 0, 2, 4, or 6 two-second trials of the baseline task (odd/even number judgments). Five to 10 minutes after studying all 175 words, participants took a recognition memory test outside the scanner for all 175 studied words and 175 novel foils. After each old/new decision (item memory), participants rated their confidence in that decision on a 1-3 scale. If participants endorsed the word as "Old", they were also asked whether the word was learned in association with an Indoor or an Outdoor image (source memory). This decision was also followed by a 1-3 confidence judgment. In the Figure, "Dirty" and "Happy" were endorsed as "Old," and participants were therefore asked to make a source memory judgment. "Pretty" was endorsed as "New," and participants were therefore not asked to make a source memory judgment.

image. After four seconds the cross turned red, and participants rated their success at forming an image (0 = “Unsuccessful”, 1 = “Partially successful”, 2 = “Successful with effort”, 3 = “Successful with ease”). Words assigned a 0 success rating were removed from subsequent analysis (9.2 ± 1.7 words per subject). Between each word presentation, participants were given 0, 2, 4 or 6 trials of a baseline task (2 sec each) in which they saw a single digit (1-9) and made an odd/even judgment. This baseline task is known to result in relatively little medial temporal lobe activity (Stark and Squire, 2001). A short break (about 1 minute) occurred after each group of 25 words.

After scanning (5-10 minute delay), participants took a recognition memory test. Three-hundred fifty words (175 studied words and 175 novel foils) were presented one at a time. For each word, participants made an Old/New judgment (Item memory) and gave a confidence rating for their judgment (1 = “Not Sure”, 2 = “Somewhat sure”, and 3 = “Very sure”). If a word was endorsed as “Old”, participants were also asked whether the word was learned in association with an Indoor or an Outdoor image (Source memory), and they gave a confidence rating for that judgment as well (on the same 1-3 scale). The test was self-paced.

fMRI imaging parameters

Imaging was carried out in a 3T GE scanner at the Center for Functional MRI (University of California, San Diego). Functional images were acquired using a gradient-echo, echo-planar, T2*-weighted pulse sequence (TR = 2 sec, two shots per

TR, TE = 30, Flip angle = 70^{o}, Bandwidth = 250 MHz). Twenty sections covering the whole brain were acquired perpendicular to the long axis of the hippocampus (4 x 4 x 7 mm voxels). High-resolution (1 x 1 x 1 mm^3) T1-weighted, magnetization-prepared rapid gradient echo (MP-RAGE) anatomical images were also collected for each participant after the first 100 study words had been presented.

fMRI image processing

Using the AFNI suite of programs (Cox, 1996), data from each run of 25 words were reconstructed, temporally aligned, co-registered using a 3D registration algorithm, and concatenated into a single file that included all 175 study words. Voxels outside of the brain were eliminated from the analysis by a threshold mask of the fMRI data. Study words were then classified into one of four groups according to subsequent performance on the recognition test: (1) Remembered words (studied words later endorsed as studied, irrespective of the source memory judgment); (2) Forgotten words (studied words later endorsed as new); (3) Item & Source words (studied words later endorsed as old that were also assigned correct source memory judgments); and (4) Item Only words (studied words later endorsed as old but assigned incorrect source memory judgments). For data analysis, two general linear models (GLM) were constructed using multiple-regression analysis. Each GLM included 6 motion regressors calculated during the 3D registration process to account for head motion and 2 regressors to account for first and second-order drift in the MR signal. The first GLM also included regressors for Remembered words and Forgotten words,

while the second GLM included regressors for Item & Source words, Item Only words, and Forgotten words. All words given a confidence rating of 1 for the item memory judgment were eliminated from this analysis.

For each group of study words (Remembered words, Forgotten words, Item & Source words, and Item Only words), a hemodynamic response (relative to the baseline condition) was first estimated for the 22 seconds following the presentation of the Indoor/Outdoor cue. Data analysis was then based on the area under the hemodynamic response function from 0 to 12 seconds following the presentation of the Indoor/Outdoor cue (at about 12 seconds, the hemodynamic response function returned to baseline). Standard landmarks were defined manually on the anatomical scans as described by Talairach and Tournoux (1998). The anatomical scans and the fMRI data were then transformed into Talairach space by AFNI using nearest-neighbor interpolation. fMRI data were resampled to 2.5 x 2.5 x 2.5 mm^3 voxels, and spatially smoothed using a 4 mm FWHM Gaussian blur. These data were used for whole brain analysis. To improve alignment of the medial temporal lobe, the ROI-AL alignment method (Law et al., 2005) was also used. Briefly, regions of interest (ROIs) for the left and right hippocampal regions and the bilateral temporopolar, entorhinal, perirhinal, and parahippocampal cortices were drawn by hand for each subject, and these ROIs were used to inform the transformation to the standard atlas. This technique has been shown to increase both the anatomical accuracy and statistical power of group analyses (Stark and Okado, 2003; Miller et al., 2005). These data were used for the analysis of medial temporal lobe activity.

Voxel-wise *t*-tests (2-tailed) were then carried out across all 15 participants for both the whole brain and medial temporal lobe analyses, based on the area under the hemodynamic response function for (1) the Remembered vs. Forgotten contrast; (2) the Item & Source vs. Forgotten contrast; (3) the Item Only vs. Forgotten contrast; and (4) the Item & Source vs. Item Only contrast. Monte Carlo simulations were used to correct for multiple comparisons and to determine how large a cluster of voxels was needed in order to be statistically meaningful ($p<.05$). The cluster sizes ranged from 281 mm^3 (when the analyses were restricted to the MTL, in which case the voxels within each cluster were significant at $p<.01$) to 1078 mm^3 (when the analyses included the whole brain, in which case the voxels within each cluster were significant at $p<.03$). Within all the clusters that emerged from the four contrasts described above, we then identified activity (relative to baseline) that was correlated with Remembered words, Forgotten words, Item & Source words, and Item Only words.

Experiment 2: Memory-impaired patients

Participants

The memory-impaired patients were 4 males and 1 female (Table 10) with lesions thought to be limited to the hippocampal region (dentate gyrus, CA fields, and subiculum). GW and RS became amnesic following a drug overdose and associated respiratory failure in 2001 and 1998, respectively. KE became amnesic in 2004 following an episode of ischemia associated with kidney failure and toxic shock

Table 10. Characteristics of Amnesic Patients

Patient	Age (years)	Education (years)	WAIS-III IQ	WMS-R Attention	Verbal	Visual	General	Delay
KE	63	13.5	108	114	64	84	72	55
LJ	67	12	101	105	83	60	69	<50
RS	45	12	99	99	85	81	82	<50
GW	45	12	108	105	67	86	70	<50
JRW	38	12	90	87	65	95	70	<50

Note. The Wechsler Adult Intelligence Scale-III (WAIS-III) and the Wechsler Memory Scale-Revised (WMS-R) yield mean scores of 100 in the normal population with a standard deviation of 15. The WMS-R does not provide numerical scores for individuals who score below 50. IQ scores for J.R.W. and R.S. are from the Wechsler Adult Intelligence scale-Revised.

syndrome. JRW became amnesic in 1990 following an episode of cardiac arrest. LJ became amnesic in 1988 during a 6-month period with no known precipitating event.

Estimates of medial temporal lobe damage were based on quantitative analysis of magnetic resonance images (MRI), compared to data for 19 controls (KE, RS, GW, and JRW) or 11 controls (the female, LJ) (Gold and Squire, 2005). The volume of the full anterior-posterior length of the hippocampus and the parahippocampal gyrus were measured using criteria based on histological analysis of healthy brains (Amaral and Insausti, 1990; Insausti et al., 1998a; Insausti et al., 1998b). For each patient, the volumes of the hippocampus and parahippocampal gyrus were divided by the intracranial volume (ICV normalized) to correct for brain size. KE, LJ, RS, GW and JRW have an average bilateral reduction in hippocampal volume of 49%, 46%, 33%, 48%, and 44% respectively (all values more than 3.0 SDs below the control mean). In comparison, the volume of the parahippocampal gyrus (temporopolar cortex, perirhinal, entorhinal, and parahippocampal cortices) is reduced by 17%, -8%, 1%, 12%, and 6%, respectively (all values within 2 SDs of the control mean). On the basis of two patients (LM and WH) with similar bilateral volume loss in the hippocampus for whom detailed post-mortem neurohistological information was obtained (Rempel-Clower et al., 1996), this degree of volume loss likely reflects nearly complete loss of hippocampal neurons (also see Gold and Squire, 2005).

Additional measurements, based on four controls for each patient, were carried out for the insular cortex, fusiform gyrus, frontal lobes, lateral temporal lobes, parietal

lobes, and occipital lobes. The only volume reduction in these regions greater than 1.3 SDs of the control mean was the parietal lobe for R.S. (Bayley et al., 2005).

Two groups of 6 control subjects (CON-1, 1 female, mean age = 56.7 ± 10.3 years; CON-2, 2 females, mean age = 62.0 ± 15.4 years) also participated.

Stimuli

The word lists used in Experiment 1 were used to generate materials for Experiment 2.

Procedure

Five patients and 6 controls (Con-1) studied 25 words three times. The procedure was the same as in Experiment 1 (e.g., imagery of Indoor/Outdoor scenes during learning, intermixed odd/even digit trials). One to two minutes after the third presentation of the study list, the recognition memory test was given (25 study words and 25 foils). As in Experiment 1, when a word was endorsed as old (item memory), participants were asked whether the word was learned in association with an Indoor or Outdoor image (source memory). The patients (but not the controls) were also tested again 1-8 weeks later with a second set of words.

To match the item memory performance of controls and patients, a second group of 6 controls (Con-2) studied 100 words. The procedure was otherwise the same as described above. In this way, it was possible to ask whether patients and

controls with similar item memory performance would also exhibit similar source memory performance.

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The dissertation author was the primary researcher and author.

VI. CONCLUSIONS

We addressed the functional neuroanatomy of declarative memory function in the medial temporal lobe (MTL) and diencephalon. Specifically, we assessed the effects of brain damage on human memory function. Further, we tested whether simple dichotomies between item memory and associative memory or item memory and source memory explain the division of labor of declarative memory function within the these structures.

In Chapter II, we presented neuropsychological and neuropathological findings from three patients (NC, MG, PN). Patient NC had extensive damage to the dentate gyrus and the CA3 and CA1 fields of the hippocampus, and some damage to layer III of entorhinal cortex in the absence of diencephalic damage. In patient MG, a bilateral stroke damaged several nuclei of the thalamus, including the nuclei of the anterior intralaminar group of the internal medullary lamina (paracentral nucleus, central median nucleus, and centralis lateralis) and the mediodorsal nucleus (MD). Patient PN had brain damage common to alcoholic Korsakoff's syndrome, including damage to the mammillary nuclei, mammillothalamic tracts, and anterior nuclei (anterodorsal nucleus, AD; anteroventral nucleus, AV) of the thalamus bilaterally. All three patients exhibited marked impairment on tests of declarative (anterograde and retrograde) memory and performed normally on tests on nondeclarative memory and tests of other cognitive functions. Importantly, all three patients were impaired on tests of recognition memory. We demonstrated that damage to the diencephalon produces

impairments in declarative memory (including recognition memory) that are similar to the impairments produced by damage to the medial temporal lobe.

In Chapter III, we investigated methods for determining the location and extent of brain damage in living patients thought to have damage to the medial temporal lobe. We used magnetic resonance image (MRI) volumetry, the process of measuring the volume of brain regions using MRI, to determine the volume of the hippocampal region and the cortices that lie along the parahippocampal gyrus (perirhinal, entorhinal, and parahippocampal cortex) in both patients and controls. One difficulty of this approach has been that the volume of these brain regions varies widely even in the normal population. To address this problem, most studies that use MRI volumetry apply some correction (normalization) for overall brain size to volume measurements of the MTL. In Chapter III, we assessed the efficacy of three of these brain size corrections. We conclude that normalization by intracranial volume significantly reduces variability in volume measurements of the hippocampal region and parahippocampal gyrus. Other methods of correcting for overall brain size exhibit some efficacy but do not reduce variability as much as normalization by intracranial volume. Thus, when we assess the location and extent of brain damage in patients participating in studies of memory (e.g., Chapter IV and Chapter V), we normalize volume measurements of the medial temporal lobe by intracranial volume.

In Chapter IV, we investigated the proposed dichotomy between item memory and associative memory. Several studies have suggested that the hippocampal region is critically involved in memory for associations but is not important (or is less

important) in memory for single items (e.g., Kroll et al., 1997; Giovanello et al., 2003; Mayes et al., 2004; Turraziani et al., 2004; but see Stark et al., 2002; Stark & Squire, 2003). In Chapter IV, patients with damage limited to the hippocampal region took a single-item memory test and a paired-items memory test, and were impaired relative to healthy controls on both tests. When the performance of the patients was improved by allowing patients to view each word or pair of words on the study lists three times each, the patients performed like the controls on both the single-item and the associative memory tests. Thus, item memory and associative memory depend similarly on the hippocampal region.

In Chapter V, we investigated the proposed dichotomy between item memory and source memory. Several studies have suggested that the hippocampal region is critically involved in memory for source (i.e., context) but is not important (or is less important) in memory for single items (e.g., Davachi et al., 2003; Ranganath et al., 2003). In Chapter V, healthy controls studied words while inside an fMRI scanner and later took an item memory test and a source memory test. Widespread activity in the MTL (including the hippocampal region, perirhinal cortex, and parahippocampal cortex) predicted success on both the item memory test and the source memory test. We then gave similar memory tests to patients with damage limited to the hippocampal region. Patients were impaired relative to controls on both the item memory test and the source memory test. When the performance of the patients and the controls on the item memory test was matched by having controls study more words fewer times each, the performance of the two groups on the source memory test

was matched as well. Thus, item memory and source memory depend similarly on the hippocampal region.

These results support a number of conclusions. First, declarative memory depends on the MTL and diencephalic structures. Further, damage limited to the hippocampus or circumscribed lesions of the diencephalon produce impairments in recognition memory. Second, damage to the diencephalon produces impairments in declarative memory (including recognition memory) that are similar to the impairments produced by damage to the medial temporal lobe. Third, simple dichotomies of item memory vs. associative memory or item memory vs. source memory do not explain the division of labor of recognition memory function in the medial temporal lobe. This conclusion is not meant to suggest that the components of the MTL are engaged in a single, undifferentiated function. Rather, this conclusion suggests that each component of the medial temporal lobe contributes to all declarative memory functions.

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