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Working memory, long-term memory, and medial temporal lobe function

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Working Memory, Long-term Memory, and Medial Temporal Lobe Function

A Dissertation submitted in partial satisfaction of the
requirements for the degree of Doctor of Philosophy

in

Psychology

by

Annette Jeneson

Committee in charge:

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2012

The Dissertation of Annette Jeneson is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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University of California, San Diego

2012

DEDICATION

To my grandmother, Ragna.

Takk for all din varme, styrke, og støtte.

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Chapter 2, in full, is a reprint of the material as it appears in "Intact working memory for relational information after medial temporal lobe damage" in *The Journal of Neuroscience* 30: 13624–13629. Jeneson, Annette; Mauldin, Kristin; and Squire, Larry, 2010. The dissertation author was the primary investigator and author of this paper.

Chapter 3, in full, is a reprint of the material as it appears in "The role of the hippocampus in retaining relational information across short delays: The importance of memory load" in *Learning & Memory* 18: 301-305. Jeneson, Annette; Mauldin, Kristin; Hopkins, Ramona; and Squire, Larry, 2011. The dissertation author was the primary investigator and author of this paper.

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Jeneson A, Mauldin KN, Hopkins RO, Squire LR (2010) Intact working memory for objects-in-scene information after hipocampal damage: The importance of memory

load. The 40th Annual Meeting of the Society for Neuroscience, November 13-17, San Diego.

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ABSTRACT OF THE DISSERTATION

Working Memory, Long-term Memory, and Medial Temporal Lobe Function

by

Annette Jeneson

Doctor of Philosophy in Psychology
University of California, San Diego, 2012

Professor Larry Squire, Chair
Professor John Wixted, Co-Chair

Working memory has traditionally been viewed as independent of the hippocampus and related medial temporal lobe (MTL) structures. Yet, memory-impaired patients with MTL damage are sometimes impaired at remembering visual or relational information across delays as short as a few seconds. The challenge has been to understand the nature of these impairments. Discussion of the possible contribution of MTL structures to working memory has often focused on a distinction between tasks with short retention intervals (a few seconds) and tasks with longer retention intervals. Yet, questions about the possible role of the MTL in working

memory do not turn on any particular retention interval. Instead, the important distinction is between tasks where the material to be learned and maintained is within the capacity of working memory and tasks where what is to be learned exceeds capacity. When capacity is exceeded, or when material must be retrieved following the redirection of attention, performance depends in part on long-term memory, even if the retention interval is brief. In three experiments, we assessed the ability of patients with MTL damage to retain relational information (object-location associations and object-in-scene information) or visual information (colored squares) across brief delays. In all experiments, patients performed as well as controls when working memory was sufficient to support performance and they were impaired only when the task requirements exceeded working memory capacity. This pattern of results supports the idea that maintenance of relational or visual information in working memory is intact after MTL damage and that damage to the MTL structures impairs performance only when the task depends, in part, on long-term memory.

INTRODUCTION

William James (1890) distinguished two memory systems that were quite different in nature. Primary memory permits active maintenance of a limited amount of information in conscious awareness, whereas secondary memory permits passive storage of large amounts of information that "has been absent from consciousness" and can be "brought back" through recollection (James 1890, p. 647-7). In modern terms, the distinction is between immediate memory or working memory on the one hand, and long-term memory on the other. This distinction has been fundamental to understanding how the brain has organized its memory functions (Atkinson and Shiffrin 1968; Baddeley and Warrington 1970; Milner 1972; Squire 2009). When material is presented for learning, a limited amount of information can be held in immediate memory. Working memory refers to the capacity to maintain this limited amount of information through active rehearsal, usually across a relatively short time interval (Baddeley and Hitch 1974). Long-term memory refers to what can be recalled from the past when the information to be learned no longer occupies the current stream of thought, either because immediate memory capacity was exceeded or because attention was diverted from the memoranda.

Early studies of memory-impaired patients with medial temporal lobe (MTL) damage found immediate memory and working memory (sometimes referred to as short-term memory) to be intact, despite markedly impaired performance on tasks of long-term memory (Drachman and Arbit 1966; Baddeley and Warrington 1970; Milner 1972). Thus, patients with damage to MTL structures (the hippocampus and

the adjacent entorhinal, perirhinal and parahippocampal cortices) demonstrated intact immediate memory for strings of digits, words, tones, and nonsense visual patterns and shapes (Drachman and Arbit 1966; Wickelgren 1968; Baddeley and Warrington 1970; Milner 1972; Cave and Squire 1992), as well as an intact ability to maintain a limited amount of information in memory by rehearsal, even for several minutes (Milner 1972). Accordingly, the view that developed was that MTL structures are involved in the formation of long-term memory and that immediate memory and working memory are independent of these structures.

This traditional idea has recently been revisited. A number of studies have reported impaired performance after MTL damage on tasks involving delays as short as a few seconds. In addition, several neuroimaging studies have reported MTL activation during short-delay tasks involving various kinds of visual material. These findings have led to debate about the concepts of immediate memory and working memory and raised the possibility that the MTL, in addition to its established role in forming long-term memory, is needed for at least some kinds of working memory. This view has been presented in two comprehensive reviews (Ranganath and Blumenfeld 2005; Graham et al. 2010).

Chapter 1 presents a reappraisal of the view offered in these earlier reviews. The chapter reviews recent neuropsychological and neuroimaging findings and emphasizes that a major challenge for interpreting impaired patient performance on short-delay tasks (or MTL activity in healthy individuals on similar tasks) is determining when performance on the task actually depends predominantly on

working memory, and when a task imposes a sufficiently large burden on memory such that performance also depends substantially on long-term memory. The key question is whether the MTL structures are critical for retention of certain kinds of visual or relational information regardless whether the task depends on working memory or long-term memory, or whether these structures are critical only when the material to be learned exceeds working memory capacity (such that performance depends, at least in part, on long-term memory).

Chapters 2, 3, and 4 presents three studies that addressed this question by assessing the ability of MTL patients and age-matched controls to retain different kinds of visual or relational material across brief delays.

In the first study (Experiments 1A and 1B; Chapter 2), participants attempted to maintain varying numbers of object-location associations across a 1-s retention interval. If the MTL structures are critical for retaining relational information regardless whether performance depends on working memory or long-term memory, then patients should be impaired even when only a small number of object-location associations needed to be maintained (and controls perform without error). Alternatively, if these structures are critical only when the memory load is large enough to exceed working memory capacity, patients should perform similarly to controls when only a small number of object-location associations needed to be maintained, and they should exhibit an abrupt discontinuity in performance at larger set sizes (where controls begin to make significant errors).

In the second study (Experiments 2A and 2B; Chapter 3), participants attempted to retain the same object-in-scene information over a brief delay in two tasks that differed in terms of the memory load. In one task, which used a continuous recognition format, participants needed to try to hold up to 9 scenes in mind, even when no scene intervened between the study scene and the corresponding test scene. In a second task, using a conventional study-test format, participants needed to hold in mind only one scene at a time for either 3 s or 14 s. If retention of relational information is critically dependent on the MTL, then the patients should be impaired even in the condition that place minimal demands on memory (3-s delay in the conventional study-test format).

In the third study (Experiment 3; Chapter 4), participants attempted to maintain 1, 2, 3, 4, or 6 colored squares across delays of 1, 3, 4, or 8 s. The main question of interest was whether patients and controls have the same visual working memory capacity (i.e., whether their performance is the same after the 1s delay typically used to assess capacity). Another question of interest was how well patients and controls were able to maintain both small and large array sizes (i.e., array sizes within as well as above their capacity limit) across longer delays.

CHAPTER 1

Working memory, long-term memory, and medial temporal lobe function

When does a task depend on working memory?

Working memory cannot be operationally defined in terms of any particular retention interval. Instead, working memory involves the process of active maintenance of a limited amount of information. The key factors that determine whether working memory is sufficient to support performance, or whether performance must also depend on long-term memory, are the amount of information that can be held in mind and how amenable this information is to active rehearsal. If the capacity of working memory is exceeded, or if material cannot be effectively maintained by rehearsal (as can be the case for nonverbal material), performance must depend in part on long-term memory, even at short retention intervals.

Long-term memory is also needed to support performance as soon as attention is diverted, even when the amount of material to be learned is limited and even when it is amenable to rehearsal. Attention can be diverted either through "the passage of time (with its endogenous and exogenous distractions) or a purposely induced distraction" (Drachman and Arbit 1966, p. 58). Because the probability that attention will be diverted increases with the amount of time that has passed since learning, long-term memory is often needed to support performance on tasks involving long delays. Similarly, because a short retention interval reduces the

probability that attention will be diverted, working memory is sometimes sufficient to support performance in tasks involving short delays so long as the amount of information to be maintained is not too great. Still, a limited amount of information may be held in mind indefinitely if attention is continuously directed towards the memorandum. At the same time, the same information can be lost from working memory even after a short interval if attention is diverted (Drachman and Arbit 1966; Milner 1972).

William James' (1890) distinction between primary memory (immediate memory) and secondary memory (long-term memory) did not emphasize the learning-test interval as an important factor. He distinguished a limited-capacity, impermanent memory system from a large-capacity, permanent storage system:

> [A]n object of primary memory … never was lost … [but] comes to us as belonging to the rearward portion of the present space of time, and not to the genuine past." An object of secondary memory, by contrast, "… is one which has been absent from consciousness altogether, and now revives anew. It is brought back, recalled, fished up, so to speak, from a reservoir in which, with countless other objects, it lay buried and lost from view. (James 1890, pp. 646-7).

Drachman and Arbit's (1966) later treatment of short-term and long-term memory echoed this emphasis on capacity and did not favor any particular retention interval:

> "Short-term" memory … deals only with subspan memoranda, evanescently, as long as the subject's attention is directed towards the memorandum. Recall following redirection of attention (i.e., by sufficient distraction or delay) depends upon a more permanent

> storage mechanism. By contrast "Long-term" memory (storage) deals both with supraspan memoranda held for long or short intervals and with subspan memoranda recalled following the redirection of attention. (Drachman and Arbit 1966, p. 59).

The idea that long-term memory may be needed to support performance even when memory is tested immediately following learning of new material might seem counterintuitive. The terms subspan and supraspan material are perhaps more helpful than the terms immediate memory and long-term memory. Consider the following example. When presented with ten words and then asked to recall them, memory-impaired patients recall fewer words than controls, even if memory is probed immediately after learning. Patients recall fewer items than controls because the ten words exceed what can be held in mind. Ten words are not subspan material. The point is that long-term memory sometimes benefits performance even when memory is tested immediately after or within seconds of learning (see also Baddeley et al. 2010, 2011; Brady et al. 2011).

Impaired short-term retention of visual information after MTL damage

In several recent studies, patients with bilateral MTL damage were found to be impaired at remembering visual information across delays as short as a few seconds. Thus, impairments have been noted on tasks involving novel objects or patterns (Aggleton et al. 1992; Buffalo et al. 1998; Holdstock et al. 2000), faces (Olson et al. 2006a; Nichols et al. 2006; Ezzyat and Olson 2008), colored squares (Olson et al. 2006a), topographical scenes (Hartley et al. 2007), and tasks requiring

retention of the relations between items (Hannula et al. 2006; Olson et al. 2006b). The majority of these impairments were observed in delayed match-to-sample tasks or change-detection tasks where the delays were 4 s or longer (Aggleton et al. 1992; Buffalo et al. 1998; Holdstock et al. 2000, Olson et al. 2006a,b; Nichols et al. 2006). Impaired performance has also been noted in two continuous recognition tests where the inter-stimulus-interval was only 3 s (Hannula et al. 2006) and (less consistently) in tasks where the delays were as short as 1-2 s (Olson et al. 2006b, Experiment 2; Hartley et al. 2007; Ezzyat and Olson 2008, in one of two tasks). In most of these studies, the findings were interpreted to mean that the MTL is needed for certain kinds of working memory.

The key question is whether these findings suggest a role for the MTL in working memory or whether they reflect instances where performance is supported in part by long-term memory (even though the study-test interval is quite brief).

Retention of novel visual objects and patterns

Earlier reviews of short-term retention of visual information in memory-impaired patients (Ranganath and Blumenfeld 2005; Graham et al. 2010) highlighted findings from five studies where retention of novel, complex and difficult-to-verbalize visual material was impaired after delays of 6 – 10 s (Figure 1 of Ranganath and Blumenfeld 2005; reprinted as Figure 9 of Graham et al. 2010). Three of these studies involved patients with presumed or confirmed bilateral MTL damage (Aggleton et al. 1992; Buffalo et al. 1998; Holdstock et al. 2000). The other two

studies are less informative about MTL function. One involved unilateral surgical lesions of the MTL, but no neuroimaging data was presented to describe the lateral extent of the lesions (Owen et al 1995). In addition, the performance of the patients at the shortest delay was only modestly disadvantaged (< 10%), and it is unclear that there was a significant impairment. The other study involved a mixed group of patients and was not restricted to MTL function (Holdstock et al. 1995). The performance of the patients in these five studies, in comparison to controls, was interpreted to mean that MTL damage impaired working memory for novel visual objects. We consider the first three studies and suggest a different interpretation of the data.

In the first study (Aggleton et al. 1992), information about the localization and extent of the lesions (caused by viral encephalitis) was not available. It is therefore difficult to make firm conclusions from these data about the MTL. In any case, it is noteworthy that the patients performed well at the 10-s delay (our Figure 1.1A). Even though the patients as a group performed numerically worse than controls at the 10-s delay, the original report emphasized that only one of the post-encephalitic patients made any errors at this delay (Aggleton et al. 1992). Thus, the patients were, as a group, impaired only after delays of 30 s or longer (i.e., under conditions where performance most likely depended on both working memory and long-term memory).

In the second study (Buffalo et al. 1998), two patients with confirmed MTL damage exhibited intact performance at the shortest retention delay and impaired

performance at the longer delays (Figure 1.1B). At the shortest delay, 0-2 s elapsed between the last of four study items and the test item. Note, however, that because the four study items were presented serially (1 s presentation time / item) with a 1 s inter-stimulus-interval, the delay between the first study item and test was actually 6-8 s, even in the 0-2 s delay condition (average delay for all four study items at the shortest delay = 3.8 s). Similarly, at the intermediate delay (6-8 s), where patients first exhibited impaired performance, the average delay for the four study items was 11 s.

In the third study (Holdstock et al. 2000), four MTL patients exhibited fully intact performance at the three short delays (Figure 1.1C), and were impaired only at the longer delays (during which active maintenance was disrupted by a filler task). Unfortunately, Ranganath and Blumenfeld's (2005) review mistakenly illustrated not the performance of the four patients with MTL damage, but the performance of five different patients from the same study who had mixed etiologies and no evidence of damage to the MTL (our Figure 1.1D). This error, which was reproduced in the more recent review by Graham et al. (2010), may have contributed to the impression that the MTL is needed for working memory of novel visual objects, because in Figure 1D the patients performed poorly at short delays. However, the discussion should have been based on the data presented in Figure 1.1C, and these data would have suggested a different interpretation.

In the three studies just reviewed, which tested retention of novel visual objects after MTL damage, performance was intact at the shortest delay(s) and impaired only at longer delays. Intact performance at the shortest delays indicates that

immediate memory was intact. Given the limits of immediate memory capacity (typically only three to four simple visual objects can be maintained even for a delay as short as 1 s, Cowan 2001; Luck and Vogel 1997), the striking finding summarized in Figure 1.1 is not that the patients were impaired at study-test delays of 6-30 s but that they exhibited intact retention of complex, visual information at delays of 0 – 10 s.

It is also worth emphasizing that intact performance at short delays after hippocampal lesions or larger MTL lesions, and impaired performance at longer delays, has been well demonstrated in monkeys (Overman et al. 1990; Alvarez et al. 1994) and also in rats (Clark et al. 2001). The findings from humans, together with the findings from non-human primates and rats, provide no positive evidence for impaired working memory after MTL damage. Indeed, the findings are fully consistent with the traditional view that memory was impaired after delays of 6-30 s because it is difficult to maintain difficult-to-verbalize material in working memory. Accordingly, we suggest that performance at these longer delays depends in part on long-term memory and that impaired performance at these longer delays reflects impaired long-term memory.

Nevertheless, it is always possible in the case of delay-dependent memory impairments to propose an alternative perspective. Even when performance is intact at short delays, one could point to the next longest delay, where an impairment first appears, and propose that performance at that retention interval ordinarily depends on working memory. Thus, impaired performance at that interval reflects impaired

working memory. While this line of reasoning is arbitrary and without background in the literature, there is no logical objection to it. However, this interpretation is testable in any given instance, and below we methods for deciding whether impaired performance after a brief delay depends on working memory or long-term memory (see *Determining when performance depends on long-term memory*) .

Retention of familiar visual items (single faces and colors)

MTL damage has also been found to impair retention after short delays of more familiar, concrete visual stimuli. In two studies where memory for a single face was probed using a change-detection task, patients with MTL damage exhibited impaired performance after delays of 4 s (Olson et al. 2006a) and 7 s (Nichols et al. 2006). The patients in the former study were also impaired on a change-detection task that required retention of three colored squares across delays of 4 or 8 s (Olson et al. 2006a). In a third study (Ezzyat and Olson 2008), MTL damage impaired retention of a single morphed face across a delay of 1 s (in a forced-choice test but not in a yes/no test) and after a delay of 8 s (in the yes/no test but not in the forced-choice test).

In the study involving colored squares (Olson et al. 2006a), MTL patients and controls saw an array of three colored squares and then decided whether or not a designated square in a second array (presented after 4 or 8 s) had the same color as the corresponding square in the first array. The poor patient performance in this task, as well as in a similar task requiring retention of one face for 4 s, was interpreted as a

visual working memory deficit and not as a result of being given supraspan material (i.e., a long-term memory deficit), because "*most people can accurately remember four colors (Luck and Vogel, 1997), or 1.5 faces (Eng et al. 2005)*" [Olson et al. 2006a, p.1093].

It is true that previous research suggests that three or four colored squares can be maintained in visual working memory (e.g., Luck and Vogel 1997; Cowan et al. 2001; Fukuda et al. 2010). However, these estimates of immediate memory capacity were all obtained from young adults. Similarly, Eng et al. (2005) obtained a capacity estimate of 1.1-1.5 faces (with memory display durations of 500 – 3000 ms) using a sample of Harvard undergraduates. The difficulty is that the appropriate comparison group for evaluating the memory capacity of MTL patients is a group of age-matched and education-matched individuals. Typically, such a group has a mean age above 60 years and, on average, less than 16 years of education. Memory capacity is smaller for older adults than for undergraduate students (Jost et al. 2011). Furthermore, estimates of visual working memory capacity in change-detection tasks are typically obtained by assessing performance after delays of about 1 s (e.g., 900 ms in Luck and Vogel 1997; average delay of 1.1 s [average of 300, 900, and 2000 ms] in Eng et al. 2005), and therefore do not provide suitable estimates of working memory capacity in tests given after delays of 4 s or longer (as in the studies of Nichols et al. 2006 and Olson et al. 2006a). Finally, it has been demonstrated that change-detection performance is limited both by the number of items that can be maintained in memory and by the similarity between sample and test stimuli (Awh et al. 2007). When the sample-test

similarity is high, more visual detail must be maintained and the memory capacity is lower (see also Alvarez and Cavanagh 2004). It is therefore notable that in two of the studies involving faces, the inter-item similarity was high (Olson et al. 2006a and Ezzyat and Olson, 2008).

These considerations make it difficult to rule out the possibility that, for the older participants in these studies, visual working memory capacity was exceeded even when the material involved three colored squares or one face. Note that patients were intact when task requirements were less demanding and likely within the limits of working memory capacity. For example, in the Nichols et al. (2006) study, patients exhibited intact change-detection performance for colored squares at a 1-s delay. Our own recent study, discussed in Chapter 4, compared the performance of MTL patients and age-matched controls on a range of array sizes (1, 2, 3, 4, and 6 colored squares) and a range of delays (1, 3, 4, and 8 s) (Jeneson et al. 2011a). At the 1-s delay, patients performed as well as controls at all array sizes. At the longer delays (average of the three longer delays), patients performed as well as controls for small array sizes (1 and 2 items) and were impaired only for array sizes that could be expected to exceed memory capacity (3, 4, and 6 items). It seems reasonable to suppose that long-term memory benefited control performance when the largest demands were made on memory (longer delays and larger array sizes). Indirect support for this idea comes from the finding that in Nichols et al. (2006) the best predictor of the patients' ability to remember a face for 7 s was performance on

standardized tests of long-term memory, suggesting that long-term memory supported performance on this task.

In the study by Ezzyat and Olson (2008), patients exhibited intact performance at the 1-s delay in one of the two tests (in the forced-choice test but not in the yes/no test). Apart from the difficulty of knowing the capacity estimates of the highly similar faces used in this study, a difficulty also arises because the task did not involve trial-unique stimuli. The stimuli were faces selected from a series of faces in which one face was gradually morphed into another. Participants studied one face and then decided which of two faces from the same morph series more closely matched the just-seen face. The poor patient performance on this test after 1 s was interpreted to reflect impaired working memory. However, the same faces reappeared several times during testing (16 study faces repeated 6 times each across 96 trials). This arrangement allowed for the possibility that healthy controls could gain an advantage over patients through learning. There is precedence for such learning effects in controls (but not patients) in a similar task where perceptual judgments involved items that were repeated many times (Kim et al. 2011).

Retention of relational and spatial information

In two studies, MTL damage impaired retention of information about the relations between items or features, even at quite short delays (Hannula et al. 2006; Olson et al. 2006b). The first study used two continuous recognition tests to explore retention of object-in-scene information and scene-face associations across short and

long lags in patients with hippocampal damage (Hannula et al. 2006). In the test of object-in-scene information (discussed further in Chapter 3), participants attempted to remember computer-generated scenes as well as the location of objects in each scene. Patients exhibited good memory for the scenes themselves (item information) but were impaired at remembering information about the location of objects within the scenes (relational information). In the test of scene-face associations, participants attempted to remember scene-face pairs (a single face superimposed on a scene for each study trial) and then decided, after a lag of 1 or 9 items, which of three faces superimposed on a scene had been earlier associated with that scene. In both tests of relational information, patients performed worse than controls even at a lag of one item, i.e., when no stimuli intervened between study and test.

The second study (Olson et al. 2006b) used a change-detection task to assess retention of objects, locations, and object-location conjunctions across delays of 1 and 8 s in patients with MTL damage. Patients and controls studied three objects presented one at a time (1 s per stimulus; 13 ms ISI) in one of nine possible locations in a 3 x 3 grid. Each object occupied a different square in the grid. In the feature condition, participants received one of two trial types: an object presented in the center square of the grid or a dot occupying one of the nine squares. They then decided whether or not the object had just been presented or, in the case of the dot cue, whether that particular location had been occupied by any of the three objects. Thus, feature trials required retention of objects and locations (but not the relations between them). In the conjunction condition, the test trial consisted of either an

object-location combination that had been seen before (match trial) or an object-location recombination (mismatch trial, e.g., object A was presented in the location that had been occupied by object B during study). Thus, conjunction trials required retention of objects and locations *plus* the relations between them. Accordingly, and as one might expect, the relational (conjunction) condition in Olson et al. (2006b) was more difficult than the item (feature) condition. In two similar experiments, the results were that patients were intact in the feature condition and impaired in the conjunction condition. Moreover, in one experiment (Experiment 2), patients were impaired in the conjunction condition even when the study-test delay was as short as 1 s (average delay of 2 s for all three study items).

The selective impairments in retention of relational information in these two studies after short delays raised the possibility that the MTL is critical for retention of relational information, even when working memory is sufficient to support performance (Hannula et al. 2006; Olson et al. 2006b). Indeed, it was suggested that the distinction between memory for single items versus memory for the relations among items might be more fundamental for understanding hippocampal function than the traditional distinction between working memory and long-term memory (Hannula et al. 2006; Olson et al. 2006b). An alternative possibility is that memory for relational information was impaired because the demands on memory were higher in the conditions assessing memory for relations than in the conditions assessing memory for items, and that these demands on memory exceeded visual working memory capacity (Shrager et al. 2008; Jeneson et al. 2011b; Baddeley et al. 2011).

In the case of Hannula et al. (2006), the relational memory question (which required maintenance of information about the items in each scene) involved a higher memory load than the item memory question (which required maintenance only of enough information to recognize the scene as familiar). In addition, the structure of the continuous recognition test meant that even at a lag of one item, participants still needed to try to hold in mind a number of previous scenes (up to 9), because the decision to identify each item as old or new sometimes depended on as many as 9 previous items (see Chapter 3, Figure 3.1). Moreover, even though the inter-stimulus interval was only 3 s, the delay between the initial presentation of a study scene and the assessment of memory for object location was as long as 14 s. In the second task which assessed memory for scene-face associations, participants also had to try to hold in mind a number of previous scene-face pairs even at the lag of 1, because they did not know whether the next trial would consist of a new study trial, a probe trial concerning the most recently presented scene-face pair, or a probe trial concerning a scene-face pair that had been presented up to nine trials earlier. It is therefore possible (as considered by Hannula et al. 2006 and Baddeley et al. 2011) that these tasks depended on both working memory and long-term memory, even in the simplest condition (lag of 1).

We recently tested this idea in two experiments that differed in their demands on memory but that assessed retention of the same object-in-scene information (Jeneson et al. 2011b). These experiments are discussed in Chapter 3. Briefly, patients were impaired only when the memory load was high (because many scenes needed to

be held in mind or because the retention interval was long). That is, the patients were impaired only in conditions where performance depended, in part, on long-term memory. circumstances performance depends, at least in part, on long-term memory.

The study by Olson et al. (2006b) also raises questions about memory load and working memory capacity. The fact that healthy individuals can sometimes remember single features (e.g., the colors and shapes of objects) without remembering the relations between them (e.g., which color was bound to which shape) (Stefurak and Boynton 1986), suggests that retention of features plus conjunctions involves a greater memory load than remembering only the features themselves. Indeed, in studies directly comparing memory for features and memory for conjunctions, performance is typically poorer when individuals must distinguish combinations of features from recombinations of features than when they must identify single features (Mitchell et al. 2000; Olson et al. 2006b, Experiment 1; Wheeler and Treisman 2002; Treisman and Zhang 2006; Alvarez and Thompson 2009). One possibility is that detecting recombinations of features is more demanding than detecting changes in single features because recombination test trials interfere with maintenance (Alvarez and Thompson 2009) or retrieval (Wheeler and Treisman 2002) of the original feature combinations.

Given that conjunction trials are typically more difficult than single feature trials, the question remains whether the memory load in the conjunction condition in Olson et al. (2006b) was sufficiently large to exceed visual working memory capacity such that performance depended, in part, on long-term memory. Note that the serial

presentation of study items meant that, on 2/3 of the trials, one or two sample images intervened between study and test. In addition, the impairment that was observed in both Experiments 1 and 2 was observed after a relatively long delay (average delay of 9 s across all three study item positions). Both interference and delay increase the probability of distraction, and active maintenance can support good performance only so long as attention is continuously directed towards the memorandum. Note too that the impaired performance reported for patients at a 1-s delay in Experiment 2 (but not in Experiment 1) occurred despite the fact that the patients performed the same in both Experiments. Specifically, in Experiment 1, at the 1-s delay patients performed like controls. In Experiment 2, the controls unaccountably performed better than they did in Experiment 1 (even though the conjunction condition was identical in the two cases).

An additional study involving spatial information deserves mention (Hartley et al. 2007). A sample computer-generated landscape showing four hills was presented together with a four-alternative choice of landscapes (the same landscape as in the sample but depicted from a different viewpoint, and three foils that resembled the target but that depicted different landscapes). Participants tried to identify which of the four alternatives depicted the same landscape as in the target. In a second condition, a 2-s delay intervened between sample and test. All five MTL patients were impaired after the 2-s delay, and three of the five patients were impaired even in the matching task. The findings were interpreted to mean that the hippocampus is critically important for allocentric spatial processing (also see Bird and Burgess 2008).

The question is whether the complexity of the landscapes meant that the task challenged the capacity of working memory. A proposed method for determining when the requirements of a task exceed what can be maintained within immediate memory or working memory is discussed below and in Chapter 2.

Determining when performance depends on long-term memory

Across tasks involving a range of different procedures and visual materials (novel visual objects, faces, colors, and information about relations between items), MTL damage has been found to impair performance even at short delays and sometimes when relatively little material needs to be remembered. How should such findings be interpreted? Do they reflect either impaired immediate memory capacity or impaired working memory? Or do they reflect circumstances where working memory capacity has been exceeded such that performance depends, at least in part, on long-term memory? To make this determination, one needs new methods that are independent of any particular task or stimulus materials.

One method seems promising in cases where the retention interval is long enough (e.g., 8 s) to allow distraction to be introduced during the retention interval (Shrager et al. 2008). In this approach, one assesses in the same task the effect of distraction on control performance as well as the effect of MTL damage on performance. It is assumed that distraction will be disruptive for controls whenever performance depends on maintaining information in working memory. In the first application of this method, controls (but not patients) were given either distraction or

no distraction between study and test. Across tests involving names, faces, or object-location conjunctions (as in Olson et al. 2006b, discussed above), there was concordance between the performance of MTL patients and the effect on control performance of introducing distraction between study and test. Specifically, patients were intact in tasks where distraction disrupted control performance, suggesting that the patients were successful because they (like controls) could maintain information in working memory. In contrast, the patients were impaired in tasks where distraction minimally affected control performance. Controls presumably succeeded in the face of distraction in tasks where they were depending on long-term memory rather than working memory. And the patients failed in those same tasks because they could not successfully draw on long-term memory. These findings, which included data from a task like that used by Olson et al. (2006b), suggest that impaired performance was attributable to impaired long-term memory.

The method described above has the potential to disambiguate the interpretation in tasks where the retention interval is 8 s or longer (enough time for distraction to be introduced). What method can be applied in the case of tasks where the retention interval is short, e.g., 1 s? One promising approach emerges from a study of digit span in memory-impaired patients, including HM (Drachman and Arbit 1966). In that study, participants heard digit strings of increasing length. Each string was repeated until it was reported back correctly. Then, a new string of digits was presented that contained one digit more than the preceding string. Controls made their first errors with strings of eight digits, but with repeated attempts at each

string they were eventually able to repeat back as many as 20 digits. By contrast, patients with MTL damage exhibited a sharp discontinuity in performance as the string length increased. For example, patient HM repeated back 6 digits without error (his premorbid digit span) but then could not succeed at 7 digits even after 25 repetitions of the same digits (Figure 1.2).

We used this same method to assess the ability of patients with MTL damage to remember object-location associations across a 1 s delay (Jeneson et al. 2010b). These experiments are discussed in Chapter 2. To preview, the patients performed well and similarly to controls when only a small number of object-location associations needed to be remembered, but they exhibited an abrupt decline in performance at the point where capacity was exceeded. Interestingly, the capacity limit for patients corresponded to the point where controls first made errors. We suggest that controls made errors when the material to be remembered exceeded immediate memory capacity and thereby limited what could be maintained in working memory. This formulation leads to two predictions. First, if working memory is intact in MTL patients, performance should be intact in those task conditions where controls perform without error after brief delays. Second, the performance of MTL patients should become impaired as the task becomes more difficult and controls begin to make significant errors.

Summary of the patient data

The preceding sections consider a number of studies in which patients with

MTL lesions were impaired, either after quite brief retention intervals or in cases when there is no retention interval at all (e.g., judgments of simultaneously presented items). These studies have often been interpreted to mean that MTL lesions impair immediate memory (or working memory) and in some circumstances perception itself. We suggest an alternative perspective, namely, that most if not all of these studies in fact make a significant demand on long-term (or supraspan) memory. In some cases, controls have an opportunity to learn about the stimulus material as the task progresses, thereby gaining an advantage over memory-impaired patients. In other cases, the amount of test material presented likely exceeds what can be held within immediate memory. In this circumstance controls gain an advantage by drawing on their intact capacity for long-term memory (also see Baddeley et al. 2010, 2011 and Brady et al. 2011 for a similar point). We suggest two methods to help resolve the different interpretations, one suited for retention intervals of several seconds (Shrager et al. 2008) and another suited for shorter retention intervals (0 – 1 s) (Jeneson et al. 2010b).

The final sections of this Chapter consider data from neuroimaging studies, which, like the patient data, have also figured prominently in discussions of the MTL and working memory.

MTL activity in imaging tasks involving short delays

MTL activity is not typically observed in imaging studies that assess activity during working memory tasks (e.g., Courtney et al. 1996; 1997; Cohen et al. 1997;

Rypma et al. 1999; Cabeza and Nyberg 2000; Wager and Smith 2003; Todd and Marois 2004; Xu and Chun 2006). It is therefore interesting that some recent studies involving complex visual stimuli, such as faces and photographs of scenes, have reported MTL activity in association with short-delay recognition memory tasks (Mitchell et al. 2000; Ranganath and D'Esposito 2001; Stern et al. 2001; Schon et al. 2004, 2009, 2010; Ranganath et al. 2005; Nichols et al. 2006; Piekema et al. 2006; 2009; Axmacher et al. 2007; Hannula and Ranganath, 2008; Olsen et al. 2009; Toepper et al. 2010; Lee and Rudebeck 2010). Next, we consider findings like these and their possible interpretation.

MTL activity is influenced by memory load

In patient studies where MTL damage impaired performance after short retention delays, the task requirements often made substantial demands on long-term memory and exceeded what could be managed within working memory. It is therefore noteworthy that the majority of imaging studies where MTL activity was observed during a short-delay task also made large demands on memory. For example, in one study, participants were asked to form a mental image of the locations of four objects in a 3 x 3 grid, to mentally rotate the image 90 degrees, and then to maintain the rotated image across an 11-s delay (Hannula and Ranganath 2008). In another study, participants attempted to maintain three trial-unique face-face pairs, three trial-unique house-house pairs, or three trial-unique face-house pairs across an 8 – 20 s delay period (Piekema et al. 2009). In other studies where MTL

activity was observed during the maintenance of only one or two items, the tasks required the maintenance of complex visual items that are difficult to rehearse, such as faces (Ranganath and D'Esposito 2001; Nichols et al. 2006) or three-dimensional geometrical shapes (Ranganath et al. 2005). Thus, it is possible that the MTL activity in these studies occurred because the memory load exceeded immediate memory capacity, and performance depended in part on long-term memory.

Indeed, in studies that directly assessed the effect of memory load on MTL activity during short-delay tasks, MTL activity was enhanced for tasks involving greater demands on memory. Thus, Axmacher et al. (2007) noted increased activity in the left hippocampus during encoding and maintenance of four trial-unique faces, but not during the encoding or maintenance of one or two trial-unique faces (Figure 1.3). In addition, activity in the left anterior hippocampus and subiculum was greater during retrieval of four novel scenes than during retrieval of two novel scenes (Schon et al. 2009). Subsequently, this effect of memory load was also observed in entorhinal cortex and perirhinal cortex during the delay period of the same task (Schon et al. 2010). In another study, enhanced MTL activity with greater memory load was observed when participants tried to remember complex rather than simple stimuli (Lee and Rudebeck 2010). In addition, for the complex stimuli, activity was greater when participants performed a 2-back task than when they performed a 1-back task. The 2-back task (high memory load condition) required detection of stimulus repetitions that were separated by an intervening stimulus. The 1-back task (low memory load condition) simply required detection of successive stimulus repetitions.

These results were interpreted as reflecting a role for the MTL in complex spatial processing or perception as well as in working memory.

Yet, there are other ways to understand such data. First, as already mentioned, it is possible that the high memory load conditions in these studies placed too great a burden on working memory, so that performance in fact depended in part on long-term memory. Second, activity detected at the time of stimulus presentation, or shortly thereafter, could reflect incidental encoding into long-term memory. Indeed, encoding into long-term memory is a relatively automatic and continuous process (for similar suggestions about neuroimaging findings obtained near the time of stimulus presentation, see Ryan and Cohen 2004a; Zarahn et al. 2005; Olsen et al. 2009). In one study, MTL activity associated with the foils presented during a recognition test predicted subsequent performance on a second, surprise recognition test that assessed long-term retention of the foils (Stark and Okado 2003). There is in fact an abundant literature demonstrating that MTL activity at the time of learning can predict subsequent long-term memory performance (see Paller and Wagner 2002). The next section considers the relevance of this literature to neuroimaging studies of working memory.

MTL activity during and after learning as a predictor of long-term memory

As described earlier, Lee and Rudebeck (2010) found enhanced MTL activity when participants tried to remember complex stimuli rather than simple stimuli. In a separate behavioral study, they also found that subsequent recognition memory was

better for complex images – the same condition that elicited the greatest MTL activity in the corresponding fMRI experiment when the material was studied (Figure 1.4). This result raises the possibility that MTL activity observed during learning is related, not to working memory or other online processes, but to the formation of long-term memory.

Three other studies obtained similar results. Thus, activity in the parahippocampal gyrus was associated with maintenance of novel photographs across a 10 s delay (Schon et al. 2004), activity in the anterior hippocampus was associated with maintenance of complex geometrical shapes early during a 7-13 s delay period (Ranganath et al. 2005), and activity in the hippocampus was associated with maintenance of a single face across a 7 s delay (Nichols et al. 2006). In each of these cases, the MTL activity that occurred while maintaining information in memory was correlated with subsequent measures of long-term memory. In addition, in a fourth study, which required the encoding and maintenance of four face-house pairs, long-term memory success was predicted by hippocampal activity at the time of encoding (Bergmann et al. 2010). However, performance on memory tests that were interleaved during the encoding phase and that involved short retention intervals was not associated with MTL activity.

The finding of a correlation between activity during encoding and subsequent long-term memory does not of course exclude the possibility that the fMRI signal in such cases contains additional information related to working memory itself (Lee and Rudebeck 2010; Ranganath et al. 2005). Nonetheless, it is striking that the extent of

MTL activity observed at the time of encoding is influenced by the demands on memory imposed by the task, and also that the activity observed at the time of encoding correlates positively with long-term retention of the material that was presented. These observations provide only weak support for interpreting MTL activity during short-delay tasks as a reflection of the operation of working memory. Instead, this activity is more likely to reflect processes related to the formation of long-term memory.

If the MTL does not support working memory, what brain structures and brain systems are involved? A long tradition of work has identified the importance of prefrontal cortex and the cortical association areas that are involved in perceptual processing. Cells in prefrontal cortex are maximally active during the delay portion of the delayed-response task (Fuster and Alexander 1971). This finding, and much subsequent work, linked the prefrontal cortex to what was initially termed short-term memory and, in later elaborations, working memory (Goldman-Rakic 1995; Fuster 2008). One view is that the prefrontal cortex supports working memory by directing attention to task-relevant sensory signals (Postle 2006). From this perspective, retention of information in working memory is supported by sustained activity in the various brain areas that process perceptual information (Jonides et al 2005; Pasternak and Greenlee 2005; Postle 2006). For example, short-term retention (working memory) of visual stimuli was associated with sustained activity in inferotemporal cortex (Fuster and Jervey 1982). In addition, working memory for motion direction was associated with sustained activity in area MT (Bisley and Pasternak 2000; Bisley

et al. 2004), and working memory for faces was associated with sustained activity in posterior fusiform gyrus (Ranganath et al. 2004). In studies of the capacity limit for visual working memory, activity in the intraparietal sulcus and regions of occipital cortex increased up to an array size of three or four visual objects and leveled off at the point where capacity was reached (Todd and Marois 2004, 2005; Vogel and Machizawa 2004; Xu and Chun 2006). Thus, working memory is a collection of temporary capacities intrinsic to "information processing" subsystems and are under top-down control by the prefrontal cortex.

Acknowledgments

Chapter 1, in part, is a reprint of the material as it appears in "Working memory, long-term memory, and medial temporal lobe function" in *Learning & Memory* 19: 15-25. Jeneson, Annette and Squire, Larry, 2012. The dissertation author was the primary author of this paper.

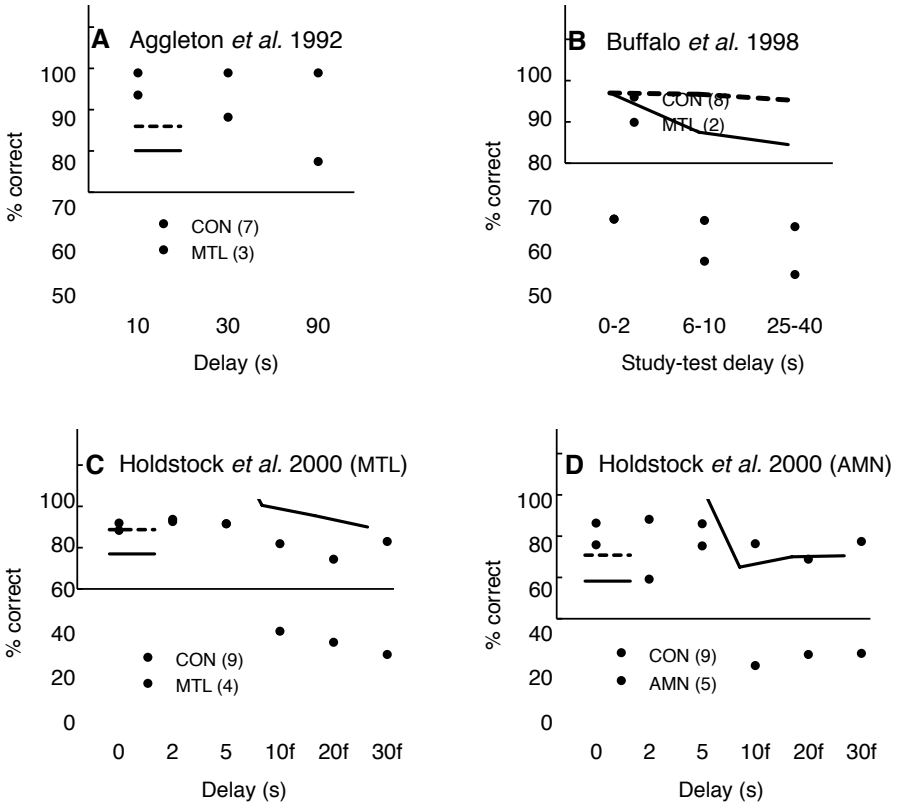

Figure 1.1. Short-term retention of novel visual objects in memory-impaired patients with: (**A**) presumed MTL damage; (**B**) and (**C**) confirmed bilateral MTL damage, and; (**D**) memory impairment from damage other than the MTL (AMN denotes amnesia). (**A**) Participants studied a detail of an abstract painting for 10 s and then, after a delay of 10, 30, or 90 s, decided which of two patterns they had seen previously. (**B**) Participants studied four kaleidoscope designs (1 s each) with a 1 s inter-stimulus interval. After a variable delay (0-2 s, 6-10 s, or 25-40 s), they decided (yes or no) whether or not a test stimulus matched one of the images just presented. (**C**) and (**D**), Participants studied a monochrome abstract pattern and then, after unfilled delays of 0 – 5 s or filled delays of 10 – 30 s, indicated from an array of 14 patterns which pattern they had seen previously. Participants included (**C**) four patients with confirmed MTL damage and (**D**) five different patients with mixed etiologies and memory impairment from damage other than the MTL. Unfortunately, two earlier reviews (Ranganath and Blumenfeld, 2005; Graham et al. 2010) presented the data from the five patients with mixed etiologies (shown here in **D**) and mistakenly labeled the patients as MTL patients. [From Jeneson et al. 2012].

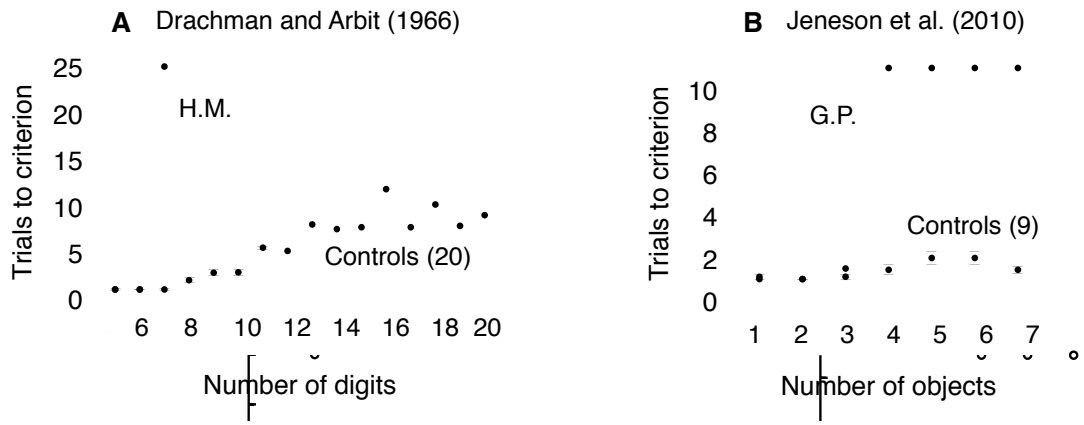

Figure 1.2. Intact working memory and impaired long-term memory. (**A**) The number of trials needed to correctly repeat back a string of digits as a function of string length. MTL patient H.M. succeeded at 6 digits in his first try but could not succeed at repeating back 7 digits even after 25 attempts with the same string. (**B**) The number of trials needed to learn the locations of different numbers of objects for MTL patient G.P. and controls. G.P. succeeded easily with 1, 2, and 3 objects but could not reproduce the locations of four objects, even after 10 attempts with the same display. Not that in both cases the patients failed at about the point when controls began to make their first errors. [From Jeneson et al. 2012].

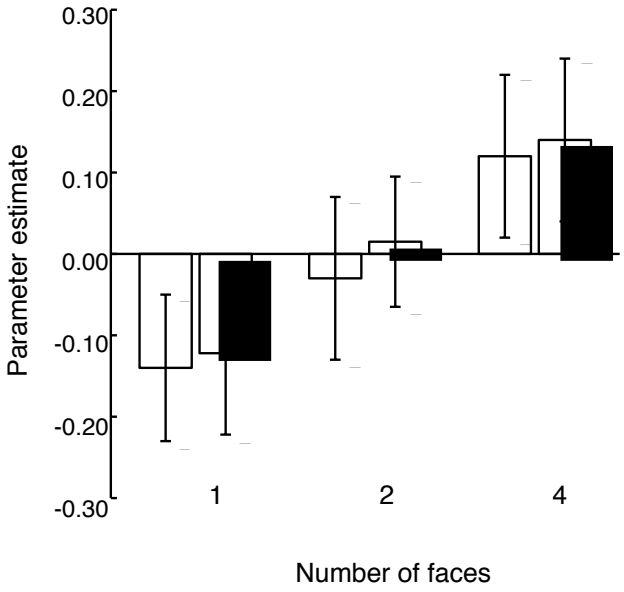

Figure 1.3. Activation in left hippocampus during encoding (white bars) and maintenance (black bars) of 1, 2, or 4 faces. Activation increased as memory load increased. Brackets show SEM. [From Jeneson et al. 2012].

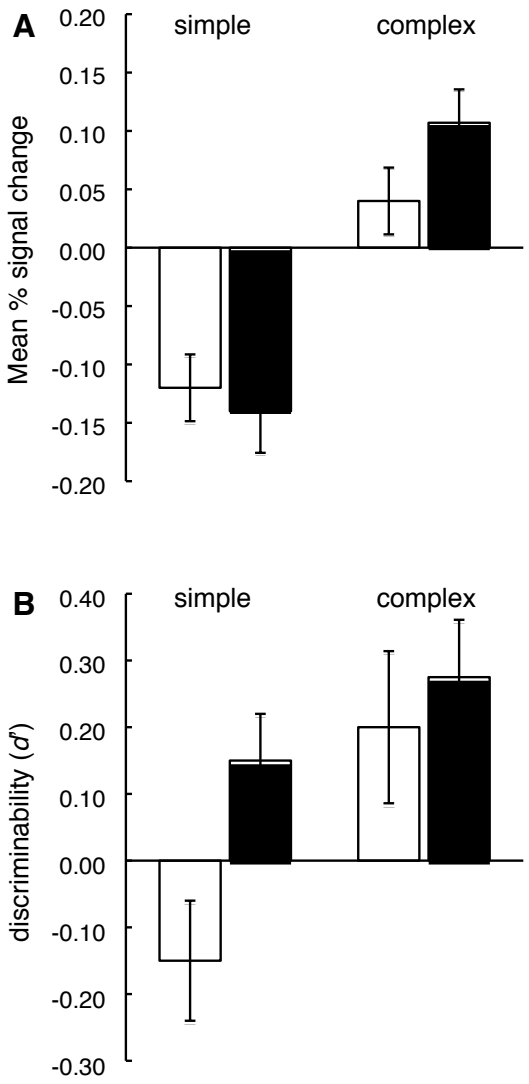

Figure 1.4. (**A**) Activity in right hippocampus during 1-back trials (white bars) and 2-back trials (black bars) with simple and complex spatial images (see text). A similar pattern of activity was observed in right parahippocampal cortex. (**B**) Eight individuals took the same test as in the fMRI experiment. After a 10-min filled delay, they then took a surprise test of long-term retention for the stimuli presented during the task. The patterns in A and B are not identical, but it is noteworthy that the different conditions of learning (simple vs. complex material; 1-back vs. 2-back testing) had similar effects on hippocampal activity during learning and on long-term behavioral memory. Brackets show SEM. [From Jeneson et al. 2012].

CHAPTER 2

Intact working memory for relational information after medial temporal lobe damage

Working memory has traditionally been viewed as independent of the hippocampus and related medial temporal lobe structures. Yet memory-impaired patients with medial temporal lobe damage are sometimes impaired at remembering relational information (e.g., an object and its location) across delays as short as a few seconds. This observation has raised the possibility that medial temporal lobe structures are sometimes critical for maintaining relational information, regardless whether the task depends on working memory or long-term memory. An alternative possibility is that these structures are critical for maintaining relational information only when the task exceeds working memory capacity and depends instead on long-term memory. To test these ideas, we drew on a method used previously in a classic study of digit span in patient HM that distinguished immediate memory from long-term memory. In two experiments we assessed the ability of four patients with medial temporal lobe lesions to maintain varying numbers of object-location associations across a 1-s retention interval. In both experiments, the patients exhibited a similar pattern of performance. They performed similarly to controls when only a small number of object-location associations needed to be maintained, and they exhibited an abrupt discontinuity in performance at larger set sizes. This pattern of results supports the idea that maintenance of relational information in working memory is

intact after damage to the hippocampus and related medial temporal lobe structures and that damage to these structures impairs performance only when the task depends on long-term memory.

Introduction

The distinction between immediate memory and long-term memory has been fundamental to understanding how the brain has organized its memory functions (Atkinson and Shiffrin 1968; Milner 1972; Squire 2009). Early studies of memory-impaired patients with medial temporal lobe (MTL) damage found immediate memory and working memory to be intact, despite markedly impaired performance on tasks of long-term memory (Drachman and Arbit 1966; Wickelgren 1968; Baddeley and Warrington 1970). Thus, working memory (the capacity to maintain temporarily a limited amount of information in mind; Baddeley and Hitch 1974) has been thought to be independent of MTL structures, whereas these same structures are essential for the formation of long-term memory.

This view has been challenged by recent reports that patients with MTL lesions are impaired on some tasks even when the retention interval is as short as a few seconds (Hannula et al. 2006; Nichols et al. 2006; Olson et al. 2006a,b; Hartley et al. 2007; Ezzyat and Olson 2008; Finke et al. 2008). These striking impairments have been interpreted as reflecting impaired working memory (sometimes termed short-term memory), especially when what has to be remembered involves relations between items (e.g., object-location associations) (Hannula et al. 2006; Olson et al.

2006b; Finke et al. 2008). Yet, as discussed by several of the authors just cited, it can be difficult to know when task performance depends on working memory and when the capacity of working memory has been exceeded such that performance depends on long-term memory.

The findings in an earlier study of digit span in memory-impaired patients (Drachman and Arbit 1966) suggest a method for making this distinction. In that study, participants heard digit strings of increasing length. Each string was repeated until it was reported back correctly. Then, a new string of digits was presented that contained one digit more than the preceding string. Controls made their first errors with strings of 8 digits and were eventually able to repeat strings as long as 20 digits. By contrast, patients with MTL damage exhibited a sharp discontinuity in performance as the string length increased. For example, patient HM repeated 6 digits correctly, but then failed at 7 digits, even after 25 repetitions of the same string. It was suggested that the patients performed normally at short string lengths because they could rely on their intact immediate memory, but they exhibited an abrupt decline in performance at the point at which immediate memory capacity was exceeded such that performance now depended on long-term memory.

In two experiments, we employed the method of Drachman and Arbit (1966) to examine memory for object-location associations after brief delays in patients with bilateral MTL damage. If working memory is intact in these patients, they should perform as well as controls at small set sizes but exhibit an abrupt discontinuity in performance at larger set sizes. Alternatively, if MTL damage impairs working

memory on some tasks, then the patients should be impaired in these tasks even at small set sizes, and even when controls perform perfectly in these conditions.

Materials and Methods

Experiment 1A

Participants

Four memory-impaired patients participated (Supplemental Table S1). Three patients have bilateral lesions thought to be limited to the hippocampus (CA fields, dentate gyrus, plus subicular complex). KE became amnesic in 2004 after an episode of ischemia associated with kidney failure and toxic shock syndrome. LJ (the only female) became amnesic in 1988 during a 6-month period with no known precipitating event. Her memory impairment has been stable since that time. GW became amnesic in 2001 following a drug overdose and associated respiratory failure. One patient (GP) has severe memory impairment resulting from viral encephalitis, together with intact perceptual and intellectual functions (Bayley et al. 2006; Shrager et al. 2006). He has demonstrated virtually no new learning since the onset of his amnesia, and during repeated testing over many weeks he does not recognize that he has been tested before (Bayley et al. 2005a).

Estimates of medial temporal lobe damage were based on quantitative analysis of magnetic resonance images compared with data for 19 controls for KE, GW, GP and 11 controls for patient LJ (Gold and Squire 2005). Nine coronal magnetic

resonance images from each patient, together with detailed descriptions of the lesions, appear in Supplemental Figure S1. KE, LJ, and GW have an average bilateral reduction in hippocampal volume of 49, 46, and 48%, respectively (all values > 3 SDs from the control mean). On the basis of two patients (LM and WH) with similar bilateral volume loss in the hippocampus for whom detailed postmortem neurohistological information was obtained (Rempel-Clower et al. 1996), this degree of volume loss likely reflects nearly complete loss of hippocampal neurons. The volume of the parahippocampal gyrus, by contrast, is reduced by 17, -8, and 12%, respectively (all values within 2 SDs of the control mean). GP has average bilateral reductions in hippocampal volume of 96%. The volume of the parahippocampal gyrus (temporopolar, perirhinal, entorhinal, and parahippocampal cortices) is reduced by 93%.

Additional measurements, based on four controls for each patient, were carried out for the frontal lobes, lateral temporal lobes, parietal lobes, occipital lobes, insular cortex, and fusiform gyrus (Bayley et al. 2005b). For all the patients, the volumes of each of these regions are within 16% of the control volumes, and none of the patients has volume reductions > 2 SDs of the control mean.

Nine controls also participated (8 males; mean age = 62.2 ± 3.2 years; mean education = 14.8 years).

Materials and procedure

The procedure was based on modifications of earlier studies of object-location

memory using arrays of toys as memoranda (Smith and Milner 1981, 1989; Crane and Milner 2005). The stimuli consisted of 60 small, nameable objects and their exact duplicates (Figure 2.1), plus two additional objects that were used for practice. On average, the objects measured 6.9 cm long, 4.0 cm wide, and 2.8 cm high.

Participants completed four test blocks, each consisting of a trial involving 1, 2, 3, 4, or 5 objects. Within each block, the first trial used one object, and then the set size was sequentially increased. Unique objects were used for each trial. At each stage, the same objects were used for all participants (e.g., a toy car was always used for a set size of one in the first block).

Before each trial, the experimenter arranged the objects in a pseudorandom pattern on a 60 cm x 60 cm white tabletop (Figure 2.1*A*). Care was taken that the objects were well distributed and that they were not arranged in an easily identifiable pattern such as a square or a straight line. In addition, no object was closer than 7 cm from the edge of the table or closer than 7 cm from any other object. Participants were instructed that they would be shown an array of objects and that they should point to each object, name each object, and study their exact locations. They were also told how much time was available for study (5 s / object). Participants then saw the array for the first time. Immediately after study, participants moved to an adjacent 60 x 60 cm white table where duplicate objects had been placed in the middle of the tabletop (~1 s retention interval). Participants were reminded that their task was to place the objects in their original locations. It was emphasized that participants should be as accurate as possible in placing the objects. There was no time limit.

Measurement of each object's displacement from its original location was calculated from photographs of the test array taken after each trial (see *Scoring*).

Before testing, participants completed practice with two objects. To emphasize the importance of accuracy, the array of two objects was presented again as needed, until both objects were placed within 5 cm of their original location.

Scoring

Before each study array was presented, the position of each object was marked on a piece of translucent Plexiglas overlaying the array. Then, after participants finished arranging the objects on each trial, the marked Plexiglas was placed over the array, and a photograph was taken and subsequently imported to Matlab ®. For scoring, the distance between each object's location at test and that same object's location at study (as marked on the Plexiglas) was measured from each photograph using the Matlab® ruler tool (Figure 2.1*B,C*). An average of these displacement scores for all the objects in the array was then calculated to yield a mean displacement score for each set size across all four blocks of the experiment.

Experiment 1B

Participants

These were the same as in Experiment 1A. Experiment 1A and Experiment 1B were administered at least 6.5 weeks apart (mean = 12.5 weeks).

Materials and procedure

The stimuli consisted of 56 small, nameable objects and their exact duplicates, plus two additional objects that were used for practice. Fifty-four of these objects were also used in Experiment 1A.

The general procedure was the same as in Experiment 1A (i.e., objects were arranged in an array in a pseudorandom pattern, unique objects were used for each trial, testing moved sequentially from small to larger set sizes, and the intra-trial interval was only ~1 s). At study, participants saw from 1 to 7 objects. At test, they again tried to place each object as it was originally. In this experiment, participants continued with study and test trials at the same set size (with the same objects and object locations) until they succeeded in reaching a criterion or failed 10 times in succession (see *Scoring*).

Controls were tested once with set sizes 1-7. Patients were tested twice with set sizes 1-7. The two test sessions were scheduled at least one week apart. Unique objects were used for each of the two tests.

Scoring

As in Experiment 1A, the position of each object at study was marked on Plexiglas. Then, after participants finished arranging the objects on each trial, the Plexiglas was placed over the array. The experimenter then placed cardboard circles (5-cm radius) on the marked locations. To reach criterion, each object in the array

needed to be in contact with its corresponding circle (i.e., the edge of each object needed to be placed within 5 cm of where it was originally centered; Figure 2.2). In this way, it could be quickly determined whether criterion had been reached on any given trial. The score was the number of trials needed to reach criterion per set size (scores averaged over two test sessions for patients). A score of 11 was given when participants failed to reach criterion after ten attempts. For some patients, the test proved so taxing that testing had to be discontinued before the largest set size was presented. In these cases, the patient average is based on the available patient data.

Results

Experiment 1A

The patients with hippocampal lesions (n=3) and patient GP with large medial temporal lobe lesions exhibited a similar pattern of performance. They performed as well as controls at small set sizes but were markedly impaired at larger set sizes. The performance of patients with hippocampal lesions (measured as mean object displacement for each set size) was intact for set sizes 1 through 3, began to decline at set size 4, and declined sharply at set size 5 (Figure 2.3A). Thus, the patients were able to maintain in memory a small number of object-location associations as well as controls, but they made substantial errors when asked to remember 5 object-location associations (mean displacement: 11.2 vs. 6.2 cm; $t_{(10)} = 4.9$, $P < .001$). The MTL patient GP performed normally at set sizes 1 and 2 but his

performance declined sharply at larger set sizes (Figure 2.3B). The pattern of results was the same when performance was measured as mean maximum displacement as a function of set size (i.e., the mean of the largest displacements in each of the four trials at a given set size).

The displacement errors made by the patients were of two kinds. Most of the errors involved placing one or more of the objects in an incorrect location that no object had occupied originally (Figure 2.1B). The other kind of error occurred when each object was placed near a location that had been occupied originally, but the locations of two (or more) objects were interchanged (Figure 2.1C). All the hippocampal patients as well as the medial temporal lobe patient GP exhibited this second kind of error (GW: 1 of 4 trials at set size 5; LJ: 1 of 4 trials at set sizes 4 and 5; KE: 1 of 4 trials at set sizes 4 and 5; GP: 2 of 4 trials at a set size of 4 and 1 of 4 trials at set size 5). One control also exhibited this second kind of error at set size 4, another control exhibited this error at a set size of 5, and a third control exhibited this error at both set sizes 4 and 5. Thus, both patients and controls did not exhibit this second kind of error until the array consisted of four objects.

We also asked whether some displacement errors occurred because participants correctly maintained the spatial relationships among the objects in the array but displaced the entire array by some amount (e.g., all objects placed seven cm below their original locations). One control exhibited this kind of error (displacing the entire array) at set size 2. No patient exhibited this error.

Experiment 1B

As in Experiment 1A, the patients with hippocampal lesions and patient GP exhibited a similar pattern of performance. They performed well at small set sizes but then declined abruptly at larger set sizes. The performance of the hippocampal patients (measured as mean number of trials needed to reach criterion at each set size) declined a little beginning at a set size of 2 and then declined sharply beginning at set size 5 (Figure 2.4A). The MTL patient (GP) performed as well as controls for set sizes 1, 2, and 3 but was unable to reach criterion for any set sizes larger than 3 (Figure 2.4B). By contrast, no control ever needed more than four trials to reach criterion, even with large set sizes. The pattern of results was similar when the displacement measure from Experiment 1 was used to assess performance (using the first trials at each set size).

By both measures (the number of trials needed to reach criterion and the mean displacement on the first trial), the performance of the patients with hippocampal lesions was variable at set sizes 2, 3, and 4 across the two test sessions. Accordingly, we examined individual performance of the hippocampal patients in each of their two test sessions (Figure 2.5). These data indicate that each patient demonstrated, in at least one test session, an ability to perform as well as controls at set sizes 1, 2, 3, and 4 (GW, session 2; LJ, session 1; KE, session 2). In addition, in every test session a sharp discontinuity appeared between the learning score obtained at small set sizes and the learning score obtained at large set sizes. Indeed, in every

session, each patient reached a set size at which they failed to reach criterion within 10 trials and, at a set size of 6 and 7, none of the patients reached criterion. Note that the test proved so taxing for patient LJ (in both sessions) and for patient KE (in one session) that testing was discontinued before the largest set size was presented.

Nearly all the errors were of the same two kinds as in Experiment 1A (i.e., one or more objects were placed in a location that no object had occupied originally, or the locations of two or more objects were interchanged). In addition, in two cases (both at a set size of 2), the patients correctly maintained the spatial relationships between the two objects but displaced the entire array by a small amount (GW for 4 of 6 trials, session 1; KE for 1 of 3 trials, session 1). Note that one control also exhibited this kind of error (displacing the entire array) at set 2 in Experiment 1A. At small set sizes (1 through 4), where the hippocampal patients sometimes did not perform as well as controls (Figure 2.5), the errors that resulted in a failure to reach criterion were typically small (displacing a single object a little outside the allowed boundary). By contrast, at set sizes 5 through 7, many of the objects in the array were typically misplaced, and the displacements tended to be large. Also, at the larger set sizes (5 through 7), all patients exhibited the second kind of error (i.e., the location of two or more objects were interchanged). This type of error was uncommon at smaller set sizes (four instances at set size 4 and one instance at set size 3). Interestingly, one control also exhibited this kind of error (interchanging objects) at set sizes 4 and 5, and another control exhibited this error at a set size of 6. Thus, with the exception of one trial in one test session (GW at set size 3), both patients and controls first

exhibited this kind of error at a set size of 4. Note that in Experiment 1A this kind of error also first appeared, for both patients and controls, at set size 4.

Discussion

We investigated the role of the hippocampus and related medial temporal lobe structures in maintenance of relational information across a short retention interval. It has been suggested that medial temporal lobe structures are sometimes critical for maintaining relational information, regardless whether the task depends on working memory or long-term memory. An alternative possibility is that these structures are critical for maintaining relational information only when the task exceeds working memory capacity and depends instead on long-term memory. To test these ideas, we assessed in two experiments the performance of four patients with medial temporal lobe damage on a task that required participants to maintain a number of object-location associations across a 1-s retention interval. In both experiments, the patients exhibited a similar pattern of performance. They performed similarly to controls when only a small number of object-location associations needed to be maintained. Furthermore, they exhibited an abrupt decline in performance when more object locations needed to be remembered.

Our findings are reminiscent of the classic observations of patient HM (Drachman and Arbit 1966). HM could repeat back strings of 1 to 6 digits without error but then failed at 7 digits even after 25 repetitions of the same digit string. The marked discontinuity in HM's performance as he moved from 6 to 7 digits was

interpreted to mean that his immediate memory capacity was exceeded when 7 digits was presented and that performance now depended on long-term memory. The abrupt discontinuity in performance that we observed suggests a similar interpretation.

Other studies of visual working memory have identified a capacity limit smaller than was found with digits and similar to what we have found here. Typically, only three to four simple visual objects can be maintained (e.g., Cowan 2001; Fukuda et al. 2010). Our data suggest a similar capacity limit on the number of object-location associations that can be maintained. Working memory capacity for visual material may be more limited than for material presented verbally and may have distinct neural substrates as well (Baddeley 2003). Nonetheless, both kinds of working memory are capacity-limited and require active maintenance.

In our task, memory for the objects themselves could potentially be maintained by both visual and verbal strategies. Memory for the spatial location of those objects presumably required maintenance by a visual strategy. First, object location memory in this task is impaired by right but not left temporal lobectomy (Smith and Milner 1981; Crane and Milner 2005). Second, in post-test interviews participants reported that they tried to retain "a snapshot" of the array.

It had been suggested previously that medial temporal lobe structures (particularly the hippocampus) are critical for maintaining relational information in some tasks, even when the task depends on working memory and retention delays as short as 3 s (Hannula et al. 2006; Olson et al. 2006b). In the first study, participants

decided whether an object in a scene had changed location compared to its location in a scene presented earlier (Hannula et al. 2006). Study trials were interleaved with probe trials that appeared either immediately after the corresponding study trial, five trials later, or nine trials later (lags of 1, 5, or 9). The patients were impaired at remembering the locations of objects even at a lag of 1 when no stimuli intervened between study and test. In the second study, participants studied three objects, each presented one at a time in one cell of a 3 x 3 grid (Olson et al., 2006b). After a delay of 1 s or 8 s, an object was presented in one of the 9 cells, and the participant decided whether it had been presented in that same location during study or whether it had been presented in a different location (i.e., a test of object-location associations). The patients were impaired even at a delay of 1 s.

In the first study (Hannula et al. 2006), it is possible that the task depended on long-term memory rather than working memory, even at a lag of 1. Specifically, the test format required participants to maintain a number of scenes in mind throughout testing, because participants did not know whether the next trial would probe a scene presented one, five, or nine scenes earlier. That is, even at a lag of 1 a substantial memory load was required in order to perform well. In the second study, patients were impaired in only one of two experiments that tested memory for three object-location associations after 1 s (Olson et al. 2006b). In our earlier study with this same procedure (Shrager et al. 2008), patients performed as well as controls at remembering up to 6 object-location associations after 1 s (see Shrager et al. 2008, for further discussion of the different findings in the two reports).

Patient GP with large medial temporal lesions exhibited the most striking demonstration of intact performance at small set sizes (Figure 2.3B; 2.4B), together with an abrupt decline in performance at larger set sizes. For example, in Experiment 1A, GP exhibited intact performance at set sizes of 1 and 2, but his performance declined abruptly at a set size of 3. In Experiment 1B, GP reached criterion as quickly as controls for 1, 2, and 3 object-location associations. When the set size was increased by only one more object (set size 4), GP failed to reach criterion even after ten attempts with the same array of objects (Figure 2.4B). This pattern of performance is strikingly similar to the pattern of performance exhibited by patient HM on the digit task (Drachman and Arbit 1966) [see Chapter 1, Figure 1.1].

The three patients with circumscribed hippocampal lesions also exhibited a pattern of performance similar to patient GP and similar to the patients in the earlier study on digit span (Drachman and Arbit 1966). In Experiment 1A, the patients exhibited intact performance at set sizes 1 to 3. Their performance began to decline at set size 4, and declined sharply at set size 5 (Figure 2.3A). In Experiment 1B, the patients exhibited a modest impairment at set sizes 1 to 4 and an abrupt decline in performance at set size 5 (Figure 2.4A).

Although in Experiment 1B the patients with hippocampal lesions did exhibit, on average, a modest impairment at small set sizes (2, 3, and 4), all the patients were able to perform as well as controls at these same set sizes in at least one of the two test sessions (Figure 2.5). In addition, at small set sizes, patient GP performed as well as controls on both test sessions of Experiment 1B. It is also true

that GP was consistently the best motivated and most attentive of all the patients. Moreover, the modest impairment apparent in the average score for the hippocampal patients (Figure 2.4A) was influenced particularly by the first test session for patient GW (Figure 2.5, upper left), and GW tended to be less careful than the others.

In summary, we explored memory for relational information (object-location associations) after a brief delay in patients with medial temporal lobe damage. Patients performed similarly to controls when only a small number of object locations needed to be maintained in memory. All patients then exhibited an abrupt decline in performance at larger set sizes. In addition, both patients and controls first made a particular type of error (interchanging the location of objects) at larger set sizes. This pattern of results supports the idea that maintenance of relational information in working memory is intact after damage to the hippocampus and related medial temporal lobe structures and that damage to these structures impairs performance only when the task depends on long-term memory.

Acknowledgments

Chapter 2, in full, is a reprint of the material as it appears in "Intact working memory for relational information after medial temporal lobe damage" in *The Journal of Neuroscience* 30: 13624–13629. Jeneson, Annette; Mauldin, Kristin; and Squire, Larry, 2010. The dissertation author was the primary investigator and author of this paper.

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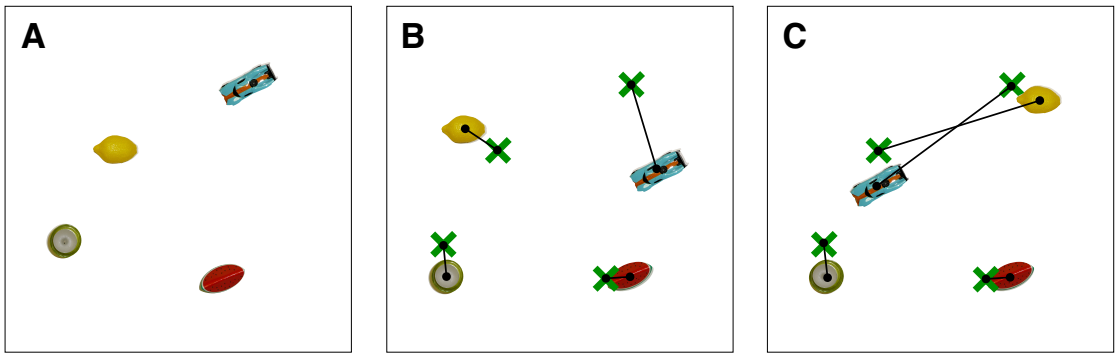

Figure 2.1. Experiment 1A. ***A***, At study, participants named the objects in an array (from one to five) and tried to memorize their exact locations. Participants then immediately moved to an adjacent table where they attempted to place the objects in their original arrangement (retention interval ~ 1 s). ***B***, A typical test trial in which a participant has attempted to place each object in its original location. The green crosses illustrate each object's original location, and the line links each cross to the location in which the object was placed at test. In this example, the displacement error involves placing one or more of the objects in an incorrect location that no object had occupied originally. ***C***, A test trial illustrating another kind of displacement error where each object is placed near a location that had been occupied originally, but the locations of two objects are interchanged. [From Jeneson et al. 2010b].

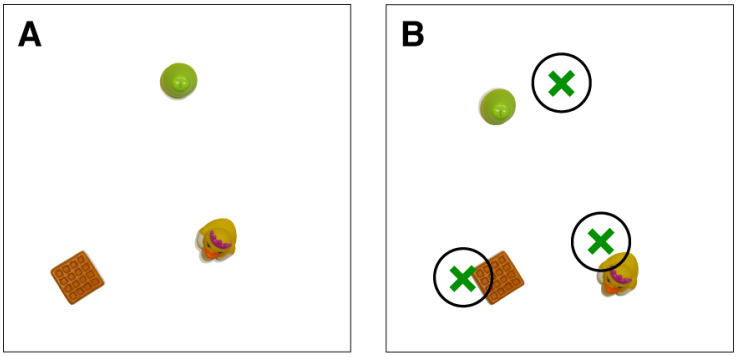

Figure 2.2. Experiment 1B. *A*, At study, participants named the objects in an array (from one to seven) and tried to memorize their exact locations. Participants then immediately moved to an adjacent table where they attempted to place the objects in their original arrangement (retention interval ~ 1 s). *B*, A typical test trial in which a participant has attempted to place each object in its original location. The green crosses illustrate each object's original location. In the trial illustrated, the participant did not reach criterion because one of the objects was placed outside the circle (5-cm radius) that defined the object's original location. [From Jeneson et al. 2010b].

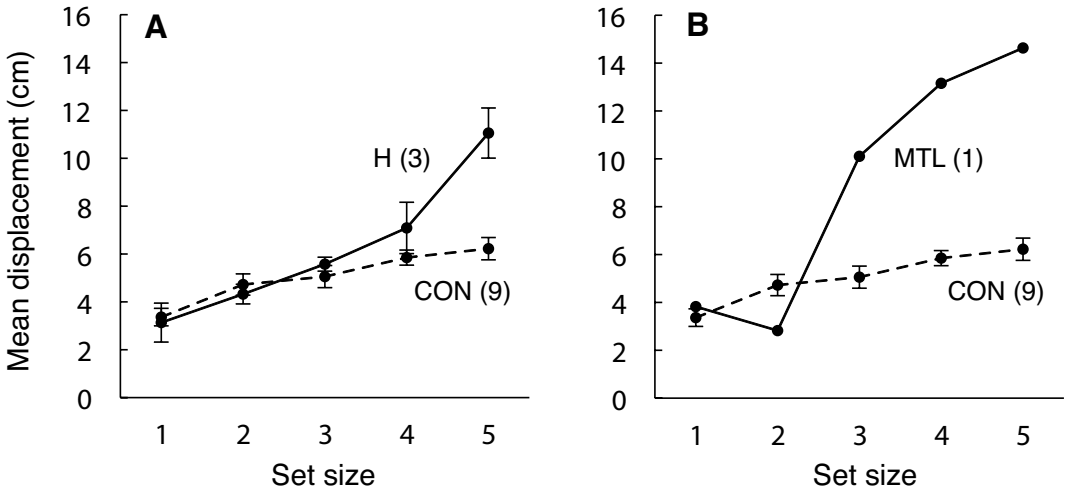

Figure 2.3. Experiment 1A. Participants saw from one to five objects in an array and then, on an adjacent table, attempted to place them in their original locations. The data show the mean distance that the objects were displaced from their original locations as a function of set size. ***A***, Patients with circumscribed hippocampal damage (H); ***B***, patient GP with large medial temporal lobe lesions (MTL); controls (CON). Error bars indicate SEM. [From Jeneson et al. 2010b].

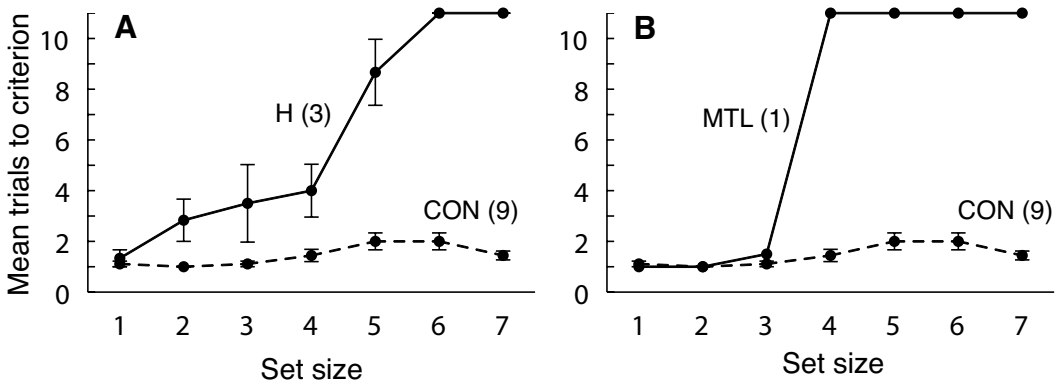

Figure 2.4. Experiment 1B. Participants saw from one to seven objects in an array and then, on an adjacent table, attempted to place them in their original locations. The data show the number of trials needed to reach criterion as a function of set size (all objects in contact with a circle [5-cm radius] around the original location). A score of 11 was assigned if criterion was not reached within 10 trials. ***A***, Patients with circumscribed hippocampal damage (H); ***B***, patient GP with large medial temporal lobe lesions (MTL); controls (CON). Error bars indicate SEM. [From Jeneson et al. 2010b].

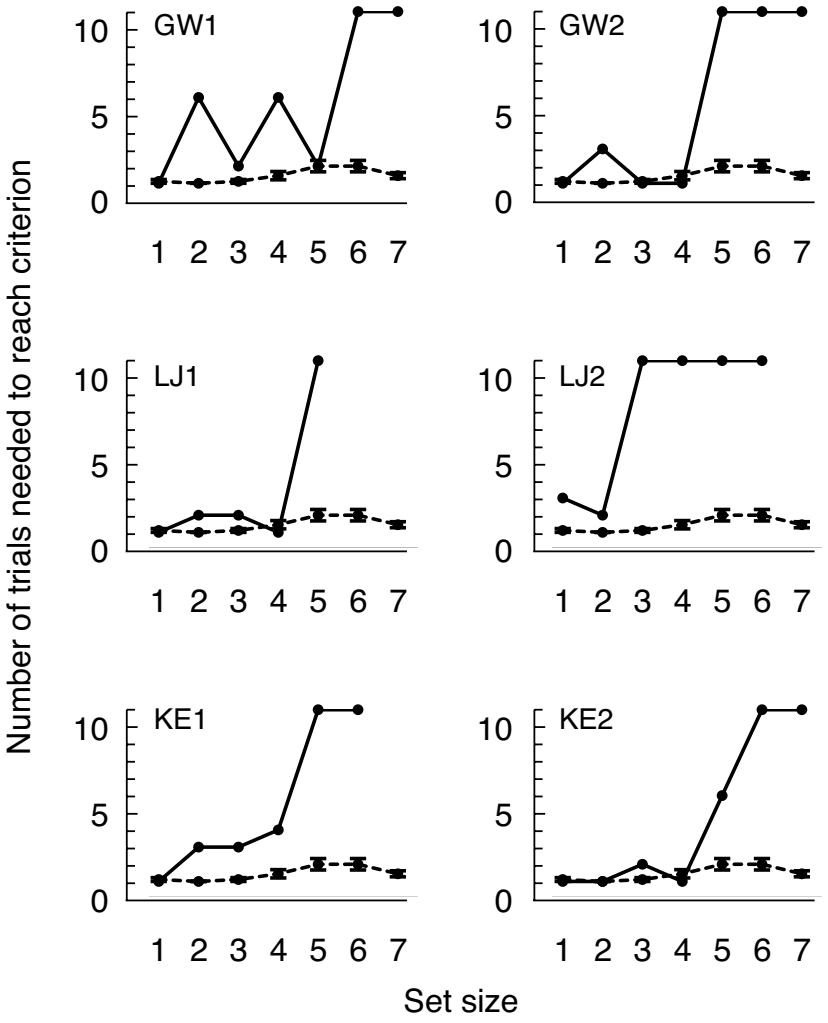

Figure 2.5. Experiment 1B. Individual patient data from Figure 2.4. Patients (solid lines) were tested twice and controls (dashed lines) were tested once. Each panel shows an individual hippocampal patient's performance on a single test session along with control performance. [From Jeneson et al. 2010b].

CHAPTER 3

The role of the hippocampus in retaining relational information across short delays: The importance of memory load

Patients with hippocampal damage are sometimes impaired at remembering information across delays as short as a few seconds. How are these impairments to be understood? One possibility is that retention of some kinds of information is critically dependent on the hippocampus, regardless of the retention interval and regardless whether the task depends on working memory or long-term memory. Alternatively, retention may be dependent on the hippocampus only when the task involves a memory load large enough to exceed working memory capacity. To explore these possibilities, we assessed the performance of patients with hippocampal lesions on two tasks requiring retention of the same object-in-scene information across a brief delay. The tasks placed different demands on memory. In one task, which used a continuous recognition format, participants needed to try to hold up to 9 scenes in mind, even when no scene intervened between the study scene and the corresponding test scene. Patients were impaired in this condition. In a second task, using a conventional study-test format, participants needed to hold in mind only one scene at a time for either 3 s or 14 s. With this procedure, patients performed as well as controls after a 3 s delay but were impaired after a 14 s delay. We suggest that retention of object-in-scene information is dependent on the hippocampus only when working memory is insufficient to support performance (because memory load is high

or the retention interval is long). In these circumstances performance depends, at least in part, on long-term memory.

Introduction

Working memory refers to the ability to hold a limited amount of information actively in mind, usually across a brief time interval (Baddeley 2003). Early studies of memory-impaired patients with medial temporal lobe (MTL) damage, including the noted patient HM, found this ability to be spared despite their severe impairment in long-term memory (Drachmann and Arbit 1966; Baddeley and Warrington 1970; Milner 1972; Cave and Squire 1992; Squire 2009). The principle that emerged from these investigations was that working memory (sometimes termed short-term memory) is independent of the hippocampus and adjacent MTL structures. It is therefore notable that a number of recent studies have reported that patients with MTL damage can be impaired at remembering information across quite brief time intervals (Hannula et al. 2006; Olson et al. 2006 a,b; Nichols et al. 2006; Finke et al. 2008; Hartley et al. 2007; Kan et al. 2007; Piekema et al. 2007; Bird and Burgess 2008; Ezzyat and Olson 2008). In addition, functional magnetic resonance imaging (fMRI) studies have reported MTL activation during short-delay recognition memory tasks (Ranganath and D'Esposito 2001; Schon et al. 2004; Ranganath et al. 2005; Nichols et al. 2006; Piekema et al. 2006, 2010; Axmacher et al. 2007, Hannula and Ranganath 2008; Toepper et al. 2010). These observations have raised the possibility that working memory may sometimes depend on the MTL.

While the emerging fMRI literature does implicate a role for the MTL in some tasks involving brief retention intervals, it is less clear whether the findings implicate a role for the MTL in working memory. For example, it has been noted that MTL activity may reflect incidental encoding of or rehearsal of novel items in support of long-term memory rather than activity needed for active maintenance of information in working memory (e.g., Ryan and Cohen 2004a; Zarahn et al. 2005; Olsen et al. 2009). If the fMRI findings can be understood without requiring a role of the MTL in working memory, how then should we understand the striking observations of impaired performance after MTL damage in tasks with delays as short as a few seconds?

In one study that explored recognition memory, patients with hippocampal damage performed well at remembering scenes but were impaired at remembering information about the locations of objects in a scene. The impairment in object-location information was evident even at the briefest delay when no stimuli intervened between study and test (i.e., memory was impaired even at a lag of one item in a continuous recognition test format) (Hannula et al. 2006). One possibility is that maintenance of information about objects in scene is critically dependent on the MTL, regardless whether performance must span short or long delays and regardless whether performance depends on working memory or long-term memory (Hannula et al. 2006). If so, the nature of the task (e.g., object-in-scene memory vs. scene-only memory) might be more fundamental for understanding hippocampal function than the classical distinction between working memory and long-term memory.

It is also possible that impaired memory performance across brief time intervals sometimes occurs because working memory capacity has been exceeded. Two important factors that influence working memory capacity are the amount of information that can be held in mind and how amenable this information is to active rehearsal. These considerations imply that the capacity of working memory can sometimes be exceeded, even at short retention intervals. For example, when presented with ten word pairs and asked for immediate recall, memory-impaired patients recall many fewer word pairs than controls (0 or 1 pair vs. 5 or 6 pairs). Perhaps (as considered by Hannula et al. 2006), an impairment in object-in-scene memory at a lag of one item could mean that the capacity of working memory was exceeded. Indeed, even at a lag of one item, participants in the earlier study still needed to try to hold in mind a number of previous scenes (up to 9), because the decision to identify each item as old or new depended on as many as the previous 9 items. In addition, there was a delay of 14 s between the initial presentation of a study scene and the assessment of memory for object location.

We conducted two experiments. In the first experiment, we used the same procedure as was used previously (Hannula et al. 2006). In the second experiment, we used a conventional test paradigm consisting of successive study-test trials that involved either a brief (3 s) or a relatively long (14 s) retention interval. For this test procedure, participants were required to hold in mind only one scene at a time. If maintenance of object-in-scene information is critically dependent on the

hippocampus, hippocampal damage should impair performance at the 3 s retention interval, even in a conventional test paradigm.

Methods and Results

Five memory-impaired patients participated (4 men) (Table S1), all of whom have bilateral lesions thought to be limited to the hippocampus (CA fields, dentate gyrus, and subicular complex). Detailed descriptions of these patients are provided in Jeneson et al. (2010a) [and in Chapter 4]. Nine coronal images from each of the six patients appear in Figure S1, and characteristics of the patients appear in Table S1. Estimates of medial temporal lobe damage were based on quantitative analysis of magnetic resonance (MR) images (Gold and Squire 2005; Bayley et al. 2005). Nine coronal magnetic resonance images from each patient, together with detailed descriptions of the lesions, are presented as supplemental material (Supplemental Figure S1). Nine controls also participated (8 males; mean age = 58.4 years; mean education = 14.0 years).

The procedure for Experiment 2A was based on an earlier study of memory for objects in scenes (Hannula et al. 2006, Experiment 1), as described in Figure 3.1. The stimuli consisted of 48 unique scenes (800 x 600 pixels) created using *Punch! home design* software (kindly provided by Dr. Hannula). Two versions of each scene were available (for a total of 96 stimuli): the original scene and a manipulated version of the scene in which the spatial relations among scene elements were changed (e.g., an urn was moved from the left side to the right side of the room; Figure 3.1).

Participants completed two blocks of trials in a continuous recognition format. Each block consisted of 24 study trials (the original scenes) interleaved with 24 test trials (12 scenes that were repeated versions of the originally studied scenes and 12 that were manipulated versions of the scenes). There were two different pseudorandom orders of scenes for each block of 48 trials. For each participant, (a) an equal number of repeated and manipulated probe trials were presented at each lag; (b) the critical item was equally often at the left or right in the scene, and (c) at each lag, the orienting question was equally likely to be associated with a 'yes' (or 'no') response.

The score for the question about whether any items had changed location was calculated as follows: (hit rate + correct rejection rate) / 2, where hit rate refers to the percent of test scenes that were correctly identified as altered and the correct rejection rate refers to the percent of scenes that were correctly identified as unaltered. Trials were scored only when the "yes" response to the first question was correct and when the response to the orienting question was also correct (orienting question: patients with hippocampal lesions, 99.2% correct; controls, 98.4% correct).

The patients were modestly impaired at answering the first yes/no question about whether a scene had been presented earlier in the block (Table 3.1). Overall, the patients scored 88.3 ± 3.5% correct at classifying the scene as old or new, and the controls scored 99.6 ± 0.2% correct ($t[4.0] = 3.26$, $p = .03$, unequal variance t-test). The result was the same when the data were analyzed using d' scores (2.8 vs. 4.1 for patients and controls, respectively; $t[4.0] = 6.13$, $p = .004$, unequal variance t-test).

The patients were also impaired at answering the second yes/no question about whether any items in the scene had changed location (Table 3.1; Figure 3.2A). An analysis of variance (ANOVA) for lag (1, 5, or 9) and group (patients with hippocampal lesions vs. controls) revealed an effect of group (F[1, 12] = 26.2, p < .001) as well as an effect of lag (F[2, 24] = 6.9, p = .004) but no lag x group interaction (F[2, 24] = 1.9, p = .17). The hippocampal patients were impaired at all three lags (ts[12] > 2.8, ps < .02). The result was the same when the data were analyzed using *d'* scores (patients = 1.60, 0.93, and 0.49; controls = 2.52, 2.10, and 2.20, for lags of 1, 5, and 9, respectively; all ts[12] > 2.6, ps < .03).

Experiment 2B was based on Experiment 2A but used a more conventional procedure to test memory for scenes (Figure 3.3). The stimuli consisted of the same 48 scenes as in Experiment 2A plus 48 new scenes created by us using the same software as in Experiment 2A. Ninety-six manipulated versions of each scene were also used, 48 from Experiment 2A and 48 new scenes created by us. Participants completed eight test blocks in a single session (12 study-test trials / block). The study-test delay was the same (3 s or 14 s) for all 12 trials in a block, and the delay alternated from block to block. The scene presented after the delay was the same as the studied scene on half the trials and was altered on half the trials. Two different versions of the test were available so that, across participants, each scene was equally likely to be repeated or manipulated. In addition, across participants, each scene was equally likely to be tested after a 3 s and a 14 s delay. The interval between

Experiment 2A and Experiment 2B was at least six weeks (mean = 22.6 weeks). Experiment 2A always preceded Experiment 2B.

The patients performed well at the 3 s delay when deciding whether any items had changed location, but they were impaired at answering the same question after the 14 s delay (Figure 3.2B) (3 s delay: $t[4.1] = 1.3$, $p = .28$, unequal variance t-test; 14 s delay: $t\,[5.0] = 3.9$, $p = .01$, unequal variance t-test). As in Experiment 2A, trials were scored only when the participant gave a correct response to the orienting question (both hippocampal patients and controls scored 97.1% correct).

The fact that the group means differed at all at the brief (3 s) delay was due to one patient who scored 85.0% correct. The mean score of the other four patients was 96.3% correct (controls = 97.4% correct). The results were the same when the data were analyzed using *d'* scores (at 3 s, patients = 3.3; controls = 3.7, $t[12] = 1.5$, $p = .15$; at 14 s, patients = 2.1; controls = 3.4, $t[12] = 4.4$, $p < .001$).

Discussion

Experiment 2A replicated the results of an earlier study that used the same continuous recognition procedure (Hannula et al. 2006). The impairment observed with this procedure raised the possibility that the hippocampus is sometimes critical for maintaining object-in-scene information, regardless whether the task depends on working memory or long-term memory (Hannula et al. 2006; see Olson et al. 2006b and Finke et al. 2008, for similar suggestions about other kinds of tasks). An alternative possibility, also considered by the authors of the earlier study (Hannula et

al. 2006), is that impaired memory for object-in-scene information across brief time intervals sometimes occurs because performance under those conditions depends on long-term memory (also see Ryan and Cohen 2004b, for a similar suggestion).

We reasoned that the continuous recognition procedure used in the earlier study (Hannula et al. 2006) and in Experiment 2A might indeed depend on long-term memory because of the requirement that, even for memory decisions made after a lag of 1 item, participants nonetheless needed to try to be holding in mind as many as 9 earlier items. That is, participants were not only holding in mind information about the immediately preceding item, they also needed to try to hold in mind information about the previous 9 items. To test this idea, we constructed a test (Experiment 2B) in which the same object-in-scene information needed to be retained over the same brief delay. However, in this case only a single item was presented. Although patients were impaired at a brief delay in Experiment 2A, they performed well in Experiment 2B. The key difference in the two conditions was that, in Experiment 2A, participants needed to try to carry a memory load involving the previous 9 items but in Experiment 2B they needed to remember only a single item.

Note that object-in-scene memory (in Experiment 2A) was impaired but that scene memory itself (in Experiment 2A) was less impaired. It seems reasonable to suppose that the burden on working memory of maintaining object-in-scene information was greater than the burden of maintaining scene-only information. In the case of object-in-scene memory, it was necessary to remember specific details

about each scene, whereas scene-only memory required only that participants remember the general appearance of each scene.

It is notable that visual working memory is quite limited in capacity (Cowan 2001; Luck and Vogel 1997; Wheeler and Treisman 2002; Alvarez and Cavanagh 2004). Typically, in healthy, young adults, only three to four simple visual objects can be maintained (Cowan et al. 2001; Fukuda et al. 2010). Accordingly, in Experiment 2A, when as many as 9 items involving complex scenes needed to be held in mind for successful performance, it is reasonable to suppose that the task exceeded working memory capacity and that performance depended, at least in part, on long-term memory.

In several studies, patients with bilateral medial temporal lobe damage have been found to be impaired at remembering visual information over brief delays where no stimuli intervene between study and test. In some cases, impairments were observed after a delay as short as 1 or 2 s. Specifically, impairments have been noted in memory tasks for three object-location associations after 1 s and 8 s (Olson et al. 2006b), for topographical scene information after 2 s (Hartley et al. 2007), and for a single face after 1 s (Ezzyat and Olson 2008, in a forced-choice task). The question of interest is whether the impairments found after short delays reflect impaired working memory or, if working memory capacity has been exceeded, an impairment in long-term memory.

This issue has been addressed in the case of retention intervals of 8 s or longer (Shrager et al. 2008) as well as in the case of a retention interval as short as 1 s

(Jeneson et al. 2010b). Shrager et al. (2008) found concordance between the performance of patients with medial temporal lobe damage and the effect on control performance of distraction between study and test. It was assumed that distraction would be disruptive when performance depended on maintaining information in working memory. The finding was that the patients were intact on tasks in which distraction disrupted control performance, suggesting that the patients were successful when they could maintain information in working memory. In contrast, the patients were impaired on tasks in which distraction minimally affected control performance, suggesting that the patients failed when performance depended significantly on long-term memory.

To explore memory for object-location associations across delays as short as 1 s, Jeneson et al. (2010b) drew on a method suggested by the classic study of digit span in patient HM (Drachman and Arbit 1966). The task required participants to maintain up to seven object-location associations across a 1 s delay. Patients with medial temporal lobe damage performed similarly to controls when only a small number of object-location associations needed to be remembered, but they exhibited an abrupt decline in performance when as many as 3 to 4 object locations needed to be remembered. The marked discontinuity in patient performance as they moved from smaller to larger set sizes occurred at about the same set size that first produced errors in controls. Presumably, controls began making errors at this point because the material now exceeded their working memory capacity. These findings suggested that maintenance of relational information in working memory is intact in patients with

medial temporal lobe damage. The patients were impaired only when the task exceeded working memory capacity such that long-term memory now benefitted performance. This method may have useful application to other reports of impaired performance after short retention intervals.

The results of the current study are consistent with the findings of Shrager et al. (2008) and Jeneson et al. (2010b). The challenge has been to understand the impairment associated with medial temporal lobe lesions that can be observed in some tasks after brief delays. It has been suggested that the ability to form new associations is an important factor, regardless of the retention interval (Ranganath and Blumenfeld 2005; Olson et al. 2006b; Hannula et al. 2006; Finke et al. 2008). Memory load is also an important factor. A question then is whether the medial temporal lobe is required in some tasks regardless of how much material needs to be maintained (i.e., memory load), or whether the medial temporal lobe is required only when the memory load is large enough (or the retention interval long enough) such that long-term memory now benefits performance. We reasoned that, if retention of object-in-scene information is critically dependent on the medial temporal lobe, then hippocampal damage should impair performance even when the memory load is minimal (and the retention interval is short). We assessed the performance of patients with hippocampal lesions on two tests requiring retention of the same information across a brief delay. The patients were intact on the test where the memory load was minimal and the retention interval was short, but they were impaired on the test where the memory load was greater (Experiment 2A) or when the retention interval

was long (Experiment 2B). We suggest that retention of object-in-scene information is dependent on the hippocampus only when working memory is not sufficient to support performance and performance depends, at least in part, on long-term memory.

Acknowledgments

Chapter 3, in full, is a reprint of the material as it appears in "The role of the hippocampus in retaining relational information across short delays: The importance of memory load" in *Learning & Memory* 18: 301-305. Jeneson, Annette; Mauldin, Kristin; Hopkins, Ramona; and Squire, Larry, 2011. The dissertation author was the primary investigator and author of this paper.

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Table 3.1.
Performance on tests of scene memory and location memory in Experiment 2A

	Lag 1 hits	Lag 5 hits	Lag 9 hits	Overall CR	Overall % Correct
Scene memory					
Controls	99.3 (1.0)	99.7 (0.5)	99.3 (1.0)	99. 8 (0.2)	99.6 (0.2)
Patients (*n* = 5)	97.5 (1.5)	95.0 (5.0)	96.3 (3.8)	80.4 (7.4)*	88.3 (3.5)*
Location memory					
Controls	100 (0.0)	83.3 (5.5)	81.9 (4.7)	87.4 (3.6)	87.9 (2.4)
Patients (*n* = 5)	80.0 (10.2)*	54.2 (5.7)*	50.8 (15.5)*	72.2 (11.1)*	66.8 (3.5)*
	Lag 1 CR	Lag 5 CR	Lag 9 CR		
Location memory					
Controls	83.3 (4.2)	86.6 (4.9)	91.7 (3.6)	87.2 (3.6)	87.9 (2.4)
Patients (*n* = 5)	72.5 (15.0)	77.5 (11.5)	65.0 (9.8)*	71.6 (11.1)*	66.8 (3.5)*

Notes:
Mean percent hits (and SEM) at each lag, overall percent correct rejections (CR) across lags, and CRs at each lag for location memory. CRs cannot be calculated for scene memory because novel items are presented only once and have no "lag". Overall percent correct is mean percent correct across lags (overall hit rate + overall CR rate / 2).
* = significantly poorer than controls, $p < .05$.

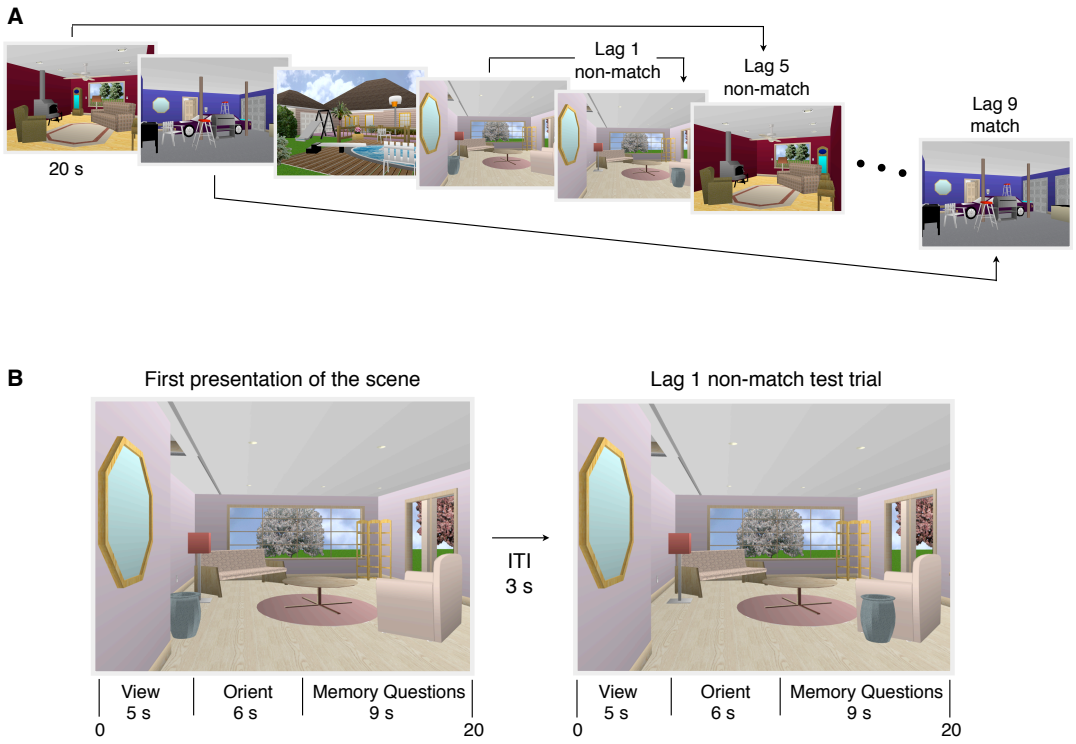

Figure 3.1. A. Experiment 2A. Repeated (match) and manipulated (non-match) test trials were interleaved systematically among study trials. Test trials appeared either immediately after the corresponding study trial (lag 1), five trials later (lag 5), or nine trials later (lag 9). The task for each scene was to decide whether the scene had appeared earlier in the series and then, critically (in the case of a "yes" response) whether any items in the scene had changed location. Note that, even for tests at a lag of 1, participants had to try to hold in mind previous scenes because they did not know whether the memory question would concern the most recently presented scene or a scene presented up to 9 items earlier. **B.** Two trials from Fig. 2.1A illustrating a lag of 1. Each scene was presented for a total of 20 s. The scene was first presented alone for 5 s. For the next 6 s the scene was presented along with an orienting question that drew the participant's attention to the item in the scene that will be moved or not moved (e.g., "*Is the urn directly under the mirror?*" [No]). Participants were not told that the orienting question identified the item that would be relevant to the memory decision. (Whenever a scene was presented a second time, the answer to the orienting question was always the same as it was when the scene was first presented. Accordingly, the answer to the orienting question did not provide information about whether the scene had been altered or not.) For the remaining 9 s of the trial the scene was accompanied by the two memory questions ("*Have you seen this scene before?*" and "*Have any items changed location?*"). Note that 14 s elapsed (3 + 5 + 6 s) between the removal of a novel scene and the first (Old/New) memory question for the next scene. [From Jeneson et al. 2011b].

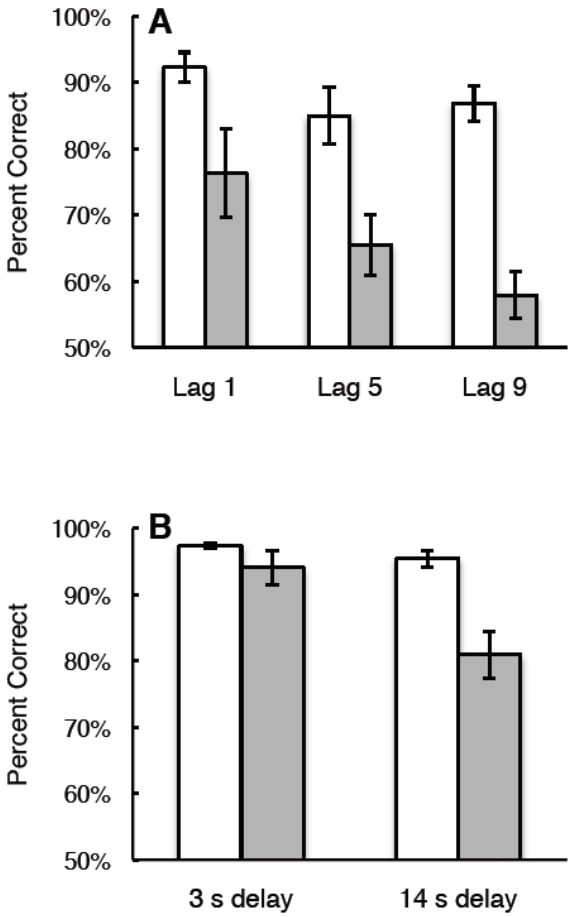

Figure 3.2. A. Experiment 2A. Performance of memory-impaired patients with hippocampal lesions (grey bars, n = 5) and matched controls (white bars, n = 9) on a test of memory for spatial relations among items in a scene. The patients were impaired at all lags. Nevertheless, they did score above chance at a lag of 1 and at a lag of 5 ((ts [4] > 3.3, ps < .02), and they scored marginally above chance at a lag of 9 (t[4]=2.30, p = .08). Error bars indicate SEM. **B.** Experiment 2B. Performance of memory-impaired patients with hippocampal lesions (grey bars, n = 5) and matched controls (white bars, n = 9). The patients performed well when memory was tested after a short (3 s) delay, but they were impaired when memory was tested after a longer (14 s) delay. Despite the marked impairment, patient performance was above chance at the 14 s delay (t[4] = 8.8, p < .001). Error bars indicate SEM. [From Jeneson et al. 2011b].

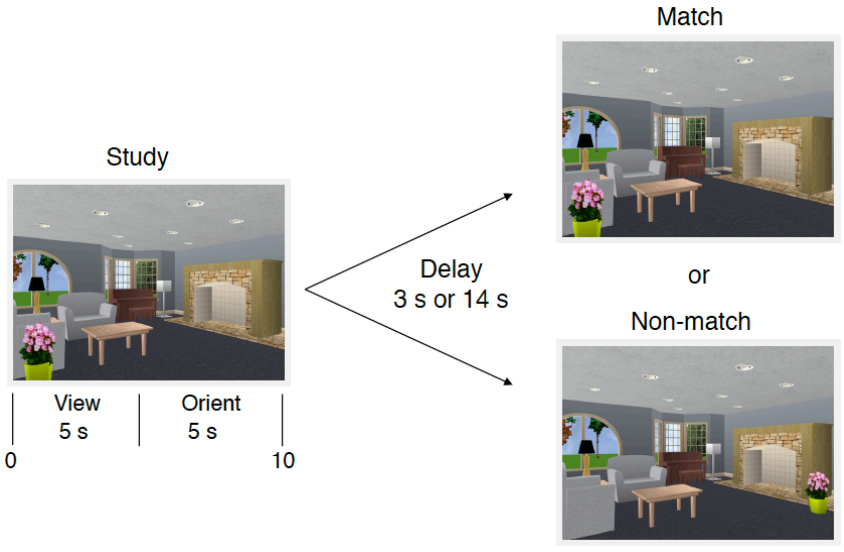

Figure 3.3. Experiment 2B. A sample study-test trial. Participants first studied the scene to the left for 5 s and then were asked an orienting question ("*Is the plant on the table?*" [No]). After viewing the scene for a total of 10 s, a delay of 3 s or 14 s intervened before either a matching or non-matching scene was presented, together with a memory question ("*Have any items changed location?*"). Only this question was asked. In the non-matching scene illustrated here, the plant has moved from left to right. [From Jeneson et al. 2011b].

CHAPTER 4

Visual working memory capacity and the medial temporal lobe

Patients with medial temporal lobe (MTL) damage are sometimes impaired at remembering visual information across delays as short as a few seconds. Such impairments could reflect either impaired visual working memory capacity or impaired long-term memory (because attention has been diverted or because working memory capacity has been exceeded). Using a standard change-detection task, we asked whether visual working memory capacity is intact or impaired after MTL damage. Five patients with hippocampal lesions and one patient with large MTL lesions saw an array of 1, 2, 3, 4, or 6 colored squares, followed after 3, 4, or 8 seconds by a second array where one of the colored squares was cued. The task was to decide whether the cued square had the same color as the corresponding square in the first array or a different color. At the 1s delay typically used to assess working memory capacity, patients performed as well as controls at all array sizes. At the longer delays, patients performed as well as controls at small array sizes, thought to be within the capacity limit, and worse than controls at large array sizes, thought to exceed the capacity limit. The findings suggest that visual working memory capacity is intact after damage to the MTL structures and that damage to these structures impairs performance only when visual working memory is insufficient to support performance.

A fundamental distinction can be drawn between immediate memory or working memory on the one hand, and long-term memory on the other. When material is presented for learning, a limited amount of information can be held in immediate memory and actively maintained in working memory (Baddeley and Hitch, 1974). Long-term memory refers to what can be recalled when the information is no longer actively maintained, either because immediate memory capacity was exceeded or because attention was diverted from the memoranda (Drachman and Arbit, 1966).

Early studies of memory-impaired patients with medial temporal lobe (MTL) damage suggested that MTL structures are involved in the formation of long-term memory and that immediate memory and working memory are independent of these structures (Drachman and Arbit, 1966; Baddeley and Warrington, 1970; Milner, 1972). Yet, recent observations of impaired performance in MTL patients on some short-delay tasks involving visual or relational information, and fMRI studies of MTL activity in healthy individuals performing similar tasks, have raised the possibility that the MTL is sometimes needed for working memory (for reviews, see Ranganath and Blumenfeld, 2005; Graham et al., 2010; but see also Jeneson and Squire, 2012).

In one study (Olson et al., 2006), patients with MTL lesions and controls saw an array of three colored squares and then decided whether or not a designated square in a second array (presented after 4 or 8 s) had the same color as the corresponding square in the first array. The poor patient performance in this task was interpreted as

a visual working memory deficit, because the material presented was thought to be within visual working memory capacity (i.e., "*most people can accurately remember … four colors (Luck and Vogel, 1997)*", Olson et al., 2006, p. 1093).

Yet, while it is true that young adults typically are able to maintain only 3 - 4 items (Cowan, 2001; Wheeler and Treisman, 2002; Vogel and Machizawa, 2004; Rouder et al., 2008; Fukuda et al., 2010, Jost et al., 2011, Sander et al., 2011), estimates from older adults (as in the Olson et al. study) are even lower (2 – 2.5 items; Jost et al., 2011; Sander et al., 2011). In addition, all of these capacity estimates were obtained when memory was assessed after delays of ~1s, not after delays of 4s or longer as in Olson et al. (2006). Accordingly, the requirement in the earlier study to maintain three items for 4 or 8s likely exceeded visual working memory capacity. Indeed, based on data presented in their Figure 5, we estimated that the controls in that study maintained about 2.3 colors across the 4s delay.

These considerations prompted two key questions. First, do MTL patients and age-matched controls have the same visual working memory capacity (i.e., is their performance the same after the 1s delay typically used to assess capacity)? Second, how well are patients and controls able to retain array sizes within (as well as above) their capacity limit across longer delays? To address these questions, we used a standard change-detection procedure but broadened the parametric space in which visual memory was probed. Specifically, we assessed the ability of patients with MTL damage to maintain 1, 2, 3, 4, or 6 colored squares across delays of 1, 3, 4, or 8 s.

Materials and Methods

Participants.

Six memory-impaired patients participated (Supplemental Table S1). Of these, five have damage thought to be limited to the hippocampus (CA fields, dentate gyrus, and subicular complex). GW and RS became amnesic after drug overdoses and associated respiratory failure. JRW became amnesic after cardiac arrest. KE became amnesic after an episode of ischemia associated with kidney failure and toxic shock syndrome. LJ (the only female) became amnesic during a 6-month period in 1988 with no known precipitating event. Her memory impairment has been stable since that time. Estimates of medial temporal lobe damage were based on quantitative analysis of magnetic resonance (MR) images compared with data from 19 controls (11 for LJ) (Bayley et al., 2005b; Gold and Squire, 2005). GW, RS, JRW, KE, and LJ have an average bilateral reduction in hippocampal volume of 48, 33, 44, 49, and 46%, respectively (all values > 3 SDs from the control mean). The volume of the parahippocampal gyrus (temporopolar, perirhinal, entorhinal, and parahippocampal cortices) is reduced by 12, 1, 6, 17, and -8%, respectively (all values within 2 SDs of the control mean).

One patient (GP) has severe memory impairment resulting from viral encephalitis. GP has demonstrated virtually no new learning since the onset of his amnesia, and during repeated testing over many weeks he does not recognize that he has been tested before (Bayley et al., 2005a). Estimates of medial temporal lobe damage were based on quantitative analysis of MR images and data from 19 controls.

GP has average bilateral reductions in hippocampal volume of 96%. The volume of the parahippocampal gyrus is reduced by 93%. Nine coronal MR images from each of the six patients are available as supplemental material in Jeneson et al. (2010a) [see Supplemental Figure S1].

12 healthy controls (8 male) served as controls for the memory-impaired patients. Controls averaged 64.3 ± 3.0 years of age and had 14.6 years of education.

Materials and procedure

The materials and procedure were modeled after the change-detection task used by Luck and Vogel (1997) and Olson et al. (2006). Each trial began with a "Get Ready" cue (500 ms) followed by a central fixation cross (300 ms). Next, an array of 1, 2, 3, 4, or 6 colored squares was presented (200 ms), followed by a second array of squares (2 sec) identical to the first or differing in the color of one square (Figure 4.1). The second array was presented after a blank retention interval of 1, 3, 4, or 8 s. In the second array, a red box surrounding one of the squares indicated which square might have changed color. The task was to decide by keypress whether the cued square had the same color as the corresponding square in the first array or whether it had a different color. In cases where the second array differed from the first (half of the trials), the cued square had a new color that was not present in the first array (i.e., the task was to decide whether a new color had been introduced, not whether a color that was present in the first array was now presented in a new location). Participants could make their response while the array was on the screen (2 s) or for 2 s after it had

disappeared from the screen. Feedback was provided after each response (the word "correct" in green for correct and the word "incorrect" in red for incorrect).

Seven colors were defined using the RGB color map matrix in Matlab®. Color intensity (for red, green, and blue) in the color map ranges from 0 to 255. The colors were specified as follows: black [1, 1, 1], white [254, 254, 254], red [255, 0, 0], green [0, 255, 0], blue [0, 0, 255], violet [200, 100, 255], and yellow [254, 254, 115]. The colored squares were presented on a gray background, and each square subtended 1.1° at a viewing distance of 50 cm. Stimuli were presented in a pseudorandom location in an invisible rectangle that subtended 17.6° x 13.2° of visual angle in the center of the screen. The minimum distance between squares was 3° of visual angle.

Participants completed two test sessions. For all but two participants, the two test sessions were separated by at least one week (mean = 10.2 ± 1.5 days). For patients RS and JRW, the two test sessions were separated by 1-2 hours. Each test session consisted of 4 trial blocks of 60 trials each. Half of the trial blocks were given in a verbal load condition and half in a no load condition (in alternating order and counterbalanced across sessions and across participants). In the verbal load condition participants were presented with two digits, presented visually on the computer screen, before the first array. They were asked to hold these digits in memory throughout the trial and then repeat them aloud at the end of the trial. In the no load condition there was no concurrent verbal load. For each condition (verbal load and no load), participants completed a total of 240 trials (4 blocks of 60 trials). Within each block of 60 trials, each unique set size/delay combination (5 set sizes x 4 delays = 20

unique trial types) was presented in groups of three trials. Thus, each unique trial type was presented three times within 60 trials and 12 times within 240 trials. Each of the 20 trial types was presented in pseudorandom order, with the constraint that the same set size or the same delay was presented for a maximum of 6 trials.

Data analysis

Performance was measured as proportion correct. To further assess capacity, we also converted the hit rates and correct rejection rates to capacity estimates using Cowan's K (Cowan, 2001). Cowan's K is a modification of an earlier method (Pashler, 1988) and estimates the number of items that are successfully held in mind (K) for each of N items in the array that are to be remembered (K = hit rate + correct rejection rate – 1) x N, where hit rate is the probability of correctly identifying a change and correct rejection rate is the probability of correctly identifying a no-change. To obtain an estimate of K across array sizes, we adopted the procedure of Alvarez and Cavanagh (2004). For each participant this procedure involves (1) averaging the K estimate across all array sizes, then (2) eliminating the array sizes smaller than this first average or greater than twice this first average, then (3) averaging the K estimates from the remaining array sizes, and (4) iterating this process until the capacity estimate no longer changes. In 19.4% of cases the estimate did not converge on a single value but oscillated between two or three estimates. In these cases we took the average of these estimates. This procedure limits the array sizes included in the capacity estimate to array sizes near each participant's capacity.

Invalid trials, in which participants did not respond within the response period, were rare (controls: 0.5% of trials; patients: 1.2 % of trials) and were not included in the analysis. Performance measures in the verbal load condition were based on all trials, regardless of performance on the concurrent digit task.

For repeated measures analysis of variance (ANOVA), Greenhouse-Geisser adjusted p-values were reported when sphericity was violated (Greenhouse and Geisser, 1959), along with the adjusted degrees of freedom.

Results

We first examined the effect of condition (no verbal load vs verbal load). As can be appreciated in Figure 4.2, the requirement in the verbal load condition to hold two digits in mind across each trial compromised both patient and control performance for the larger, but not the smaller, array sizes. Thus, an overall ANOVA (condition x array size x delay x group [controls vs hippocampal patients]) revealed an effect of group [$F_{(1, 15)} = 6.6$; $P < .05$], condition [$F_{(1, 15)} = 25.2$; $P < .001$], and array size [$F_{(4, 60)} = 95.7$; $P < .001$]. There was also a condition x array size interaction [$F_{(2.5,37.3)} = 3.6$; $P < .05$] and a group x array size interaction [$F_{(4, 60)} = 2.7$; $P < .05$]. In addition, the effect of condition was significant for both groups (controls: $F_{(1,11)} = 9.6$; $P < .05$; hippocampal patients: $F_{(1,4)} = 14.7$; $P < .05$).

Given these effects of verbal load, the main analyses assessed performance separately for the no load and the verbal load conditions. Scores for the three different delays (3, 4, and 8 s) were averaged to assess performance at the longer delays because,

for both conditions, a delay (3, 4, or 8 s) x array size x group ANOVA revealed no effect of delay and no delay x group interaction. For completeness, Cowan's K estimates for each of the four delays are provided in Table 4.1.

For each condition, we asked whether patients and controls performed similarly at the 1s delay typically used to assess capacity and whether their capacity estimates were the same. We also asked how well patients and controls were able to maintain information across delays longer than the 1s delay, and how their performance might vary as a function of array size.

At the 1s delay typically used to assess capacity, patients and controls performed similarly in both the no load (P >.9) and the verbal load condition (P >.05) (Figures 4.3 and 4.4, respectively, panels to the left). The corresponding Cowan's K estimates were also similar (Table 4.1, Ps > .2). At the longer delays, by contrast, patients performed worse than controls in both conditions (no verbal load, Figure 4.3, right: [$F_{(1, 15)}$ = 4.9; P < .05]; verbal load, Figure 4.4, right: [$F_{(1, 15)}$ = 8.3; P < .05]). The K-estimates were also lower for the patients than for the controls at the longer delays (No load: $t_{(15)}$ = 2.9, P <.05; verbal load: $t_{(15)}$ = 2.8, P <.05).

The group effect at the longer delays was due to the fact that the controls performed better than the hippocampal patients at the larger array sizes (3, 4, and 6 items; Figures 4.3 and 4.4, panels to the right). With smaller array sizes (1 and 2 items), the patients performed like controls even after longer delays. Patient GP with larger MTL lesions was impaired at the longer delays like the hippocampal patients. At the short delay, his performance was good in the no load condition (except for

array size 4; Table 4.1; Figure 4.3) and lower than controls than in the verbal load condition ($P < .01$; Table 4.1; Figure 4.4).

Interestingly, in the no load condition, with larger array sizes, the difference between patients and controls at long delays occurred because controls (but not patients) performed better after long delays than after the short delay (Table 4.1; Figure 4.3). This observation was documented by a delay (short versus long) x array size interaction for controls [$F_{(2.0, 22.4)} = 5.6$; $P < .05$] but not for the hippocampal patients (Figure 4.3). Furthermore, the K-estimates for controls in the no load condition were significantly higher at the longer delays than at the 1s delay (Table 4.1; $t_{(11)} = 2.6$, $P < .05$]). By contrast, the performance of the hippocampal patients at the 1s delay was no different from their performance at the longer delays (Figure 4.3: all *P*s for array sizes 3, 4, and 6 > .15), and their K estimate for the longer delays was marginally smaller than their K estimate for the short delay (Table 4.1; $t_{(4)} = 2.3$, $P = .08$). Although these effects for controls (better performance at the longer delays than at the short delay) did not obtain in the verbal load condition, there was a small numerical trend even in that condition for higher capacity estimates after the long delays than after the short delay (Table 4.1). As in the no load condition, the performance of the patients at the 1s delay was similar to their performance at the longer delays (Figure 4.4: all *P*s for array sizes 3, 4, and 6 > .35), and their K estimates were also similar at the short and at the longer delays (Table 4.1; $P = .3$).

Although our main analyses focused on performance on the visual change-detection task, we also examined performance on the digit task in the verbal load

condition. Overall, the hippocampal patients made more digit errors than controls (errors on 14.6 ± 6.1% of trials compared to 3.5 ± 1.6 % of trials, respectively). The MTL patient performed as well as controls (errors on 1.7 % of trials). Interestingly, both patients and controls exhibited an increase in the number of digit errors with increasing array size. The hippocampal patients made errors on 10.0, 15.4, 15.8, 13.8, and 17.9 % of trials for array sizes 1, 2, 3, 4, and 6, respectively (collapsed across the four delays). The corresponding scores for controls were 1.9, 3.3, 3.6, 3.5, and 5.2 % (see also Morey and Cowan 2004, 2005, for similar effects of total memory load on amodal interference). The greater vulnerability to interference from concurrent verbal load in patients compared to controls likely accounts for some of the difference in patient and control performance observed in the verbal load condition (see *Discussion*).

Discussion

We used a standard change-detection task (Luck and Vogel, 1997) to assess the role of the hippocampus and related MTL structures in retention of simple visual information. Patients with MTL damage (five with lesions restricted to the hippocampus; one with larger MTL lesions) and age-matched controls attempted to remember 1, 2, 3, 4, or 6 colored squares across delays of 1, 3, 4, or 8 s. At the 1s delay (in the no load condition) typically used to assess visual working memory capacity (Luck and Vogel, 1997; Vogel and Machizawa, 2004; Todd and Marois, 2004; Jost et al., 2011, Sander et al., 2011), patients performed as well as controls at all array sizes, even when performance was not at ceiling (Figure 4.3). The

corresponding capacity estimates for patients and controls at the 1s delay were also approximately the same (2 - 2.5 items with no verbal load; Table 4.1) and similar to those obtained from older adults in two recent studies (Jost et al., 2011; Sander et al., 2011). (Note that in these two studies visual working memory capacity was assessed without a concurrent verbal load.) At the longer delays, patients performed as well as controls when the number of items to be maintained was within this capacity limit (1 and 2 items), and they performed worse than controls when the number of items to be maintained exceeded this limit (3, 4, or 6 items).

Our findings replicated the previous finding (Olson et al., 2006) that patients with MTL damage are impaired at remembering 3 colored squares after 4s. In the earlier study, as well as in a number of other studies assessing short-term retention of visual information in patients with MTL damage, impaired performance has been interpreted to mean that the MTL is critical for at least some kinds of working memory (for reviews representing this view, see Ranganath and Blumenfeld 2005 and Graham et al., 2010). Yet, our findings at the 1s delay, across all array sizes (and without verbal load), demonstrate intact visual working memory capacity after MTL damage.

In the verbal load condition, both controls and patients performed worse than in the no load condition (Figure 4.2). There was a tendency for the patients to be affected by the verbal load more than the controls, though the interaction of group x load condition did not reach significance ($P = .11$). Interestingly, this tendency was also evident for patient GP (Table 4.1; Figure 4.2). GP made only 1.7% errors in the

verbal digit task (controls, 3.5%; hippocampal patients, 14.6%). His low scores in the verbal load condition may therefore reflect the particularly strong attention he directed to the digit task, thereby impairing his performance on the change-detection task itself.

Working memory involves the process of active maintenance of a limited amount of information and cannot be operationally defined in terms of any particular retention interval. If the amount of information to be maintained exceeds visual working memory capacity, or if attention is diverted, then performance depends in part on long-term memory, even at short retention intervals (Drachman and Arbit, 1966; Jeneson and Squire, 2012; see also Brady et al., 2011). In studies where the contribution of working memory and long-term memory to task performance have been formally assessed, patients with MTL damage exhibited intact performance so long as working memory was sufficient to support performance, and they were impaired only when long-term memory was also needed to support performance (Shrager et al., 2008; Jeneson et al., 2010b; for review, see Jeneson and Squire 2012).

For example, in Jeneson et al. (2010b), the task required participants to maintain up to seven object-location associations across a 1s delay. MTL patients performed similarly to controls when only a small number of object-location associations needed to be remembered, but they exhibited an abrupt decline in performance when as many as 3 to 4 object locations needed to be remembered. The marked discontinuity in patient performance as they moved from smaller to larger set sizes occurred at about the same set size that first produced errors in controls.

Presumably, controls began making errors at this point because the material now exceeded their working memory capacity. These findings suggested that active maintenance is intact in patients with MTL damage. The patients were impaired only when the task exceeded working memory capacity such that long-term memory now benefited performance. The findings in the current study are consistent with the findings of Jeneson et al. (2010b). We propose that patients were impaired only when the amount of information to be remembered exceeded visual working memory capacity (i.e., at longer delays and at larger array sizes).

What might account for the finding that, in the no load condition, controls performed better after the longer delays than after the short delay? It seems unlikely that, at the short delay but not at the longer delays, the presentation of the second array disrupted transfer of the sample array into visual working memory. It has been shown that transfer into visual working memory, measured by varying the time between presentation of the sample and an interrupting mask, does not continue beyond 200-300ms (or 50ms per item) after the onset of the sample array (Vogel et al. 2006). One intriguing possibility is that controls benefited from longer delays because these conditions enabled them to recode, elaborate, and stabilize the visual information using long-term memory (e.g., by verbally rehearsing the colors during the delay). It has been noted that longer delays (> 1s) "not only underestimate VSTM [visual working memory] capacity owing to memory degradation (Phillips, 1974), but also favour the recruitment of rehearsal mechanisms and verbal/abstract recoding of the visual material (Coltheart, 1972)" (Todd and Marois, 2004, p. 751). Thus, at the

longer delays, as participants realize that they will need to retain information for longer than ~1s, they might engage in effortful rehearsing in order to retain as much information as possible. As a result, estimates of capacity obtained by controls at these longer delays may reflect not only the limits of working memory but also the contribution of long-term memory. Consistent with this idea, it is interesting that in the verbal load condition, which could be expected to minimize verbal rehearsal and thereby reduce the contribution of long-term memory, controls exhibited little or no improvement in performance at the longer delays as compared to the 1s delay (Table 4.1; Figure 4.4).

In studies of the neural correlates of visual working memory and visual working memory capacity, the key areas that have been implicated are, not MTL structures, but intraparietal sulcus, visual cortex, and the prefrontal cortex. For example, fMRI activity in the intraparietal sulcus and areas of occipital cortex has been found to increase with increasing array size, reaching asymptote at the point where capacity is exceeded (Todd and Marois 2004, 2005; Xu and Chun, 2006). In addition, numerous findings suggest that maintenance of information in working memory is supported by sustained activity in the various brain areas that process or encode the to-be-remembered information (Jonides et al., 2005; Pasternak and Greenlee, 2005; Postle, 2006). For example, Serences et al. (2009) observed sustained activation in V1 during maintenance of the orientation or the color of a multi-feature object. This sustained activation was observed in the same regions of V1 that process the relevant sensory information (i.e., orientation or color). Other work has also

identified the importance of prefrontal cortex (Goldman-Rakic, 1995; Fuster, 2008). Cells in prefrontal cortex are maximally active during the delay portion of the delayed-response task (Fuster and Alexander, 1971). In addition, patients with unilateral prefrontal cortex lesions were impaired on a lateralized change-detection task when arrays of colored squares were presented contralateral to the lesion (i.e., when the information was presented to the damaged hemisphere) (Voytek and Knight, 2010). One possibility is that maintenance of visual information in working memory is supported by sustained activity in the same sensory areas that are involved in the encoding of the memoranda, and that the prefrontal cortex supports working memory by directing attention to task-relevant sensory signals (Postle, 2006).

In summary, we demonstrated that visual working memory capacity is intact after MTL damage (without a concurrent verbal load) and that MTL damage impairs performance after delays of 3, 4, and 8s only when the information to be held in mind exceeds the capacity limit of visual working memory (2 – 2.5 items in older adults). At these longer delays, patients performed as well as controls at array sizes below the capacity limit (1 or 2 items), and they performed worse than controls only at array sizes that exceeded the capacity limit (3, 4, or 6 items). Together with other findings (see Jeneson and Squire, 2012), these findings suggest that MTL damage impairs performance only under conditions where working memory is insufficient to support good performance. In these cases, controls gain an advantage over patients because performance can be supported by long-term memory in addition to working memory.

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Table 4.1 Cowan's K estimates of visual working memory capacity

	Short delay (1s)	3s	4s	8s	Longer delays (3, 4, and 8s)
No verbal load					
Controls	2.62 (.2)	3.66 (.4)	3.05 (.2)	3.28 (.4)	3.33 (.3)
H patients (n = 5)	2.46 (.2)	1.47 (.5)*	2.30 (.3)	1.87 (.2)*	1.88 (.3)*
MTL (GP)	2.11	1.77	1.75	2.54	2.02
Verbal load					
Controls	2.32 (.2)	2.60 (.2)	2.48 (.1)	2.43 (.2)	2.50 (.1)
H patients (n = 5)	1.93 (.2)	1.83 (.4)*	1.73 (.3)*	1.36 (.4)*	1.64 (.4)*
MTL (GP)	1.50	1.50	1.75	1.83	1.69

The Table shows the mean (and SEM) overall capacity estimates for each of the four delays and the three longer delays combined. The capacity estimates for the short (1s) delay and the longer delays correspond to the data presented in the left and the right panels of Figure 4.3 (no verbal load) and Figure 4.4 (verbal load), respectively. Asterisks indicate significant difference between patients and controls ($P < .05$).

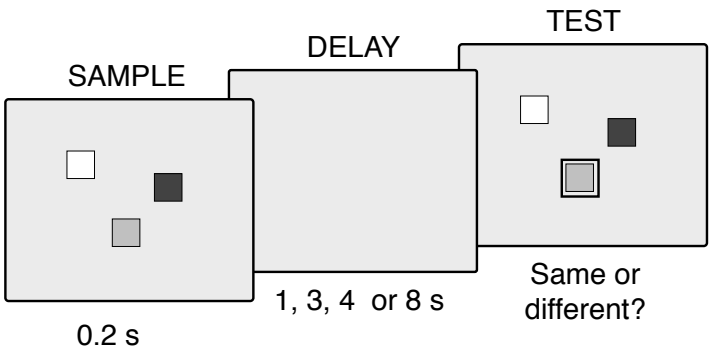

Figure 4.1. Sample stimulus array. Participants saw an array of colored squares for 200 ms (1, 2, 3, 4 or 6 squares). Following a blank retention interval of 1, 3, 4 or 8 s, participants saw the array of colored squares again. One of the squares was cued by a surrounding red box. On half the trials, the first array and the second array were identical, and on half the trials the cued square in the second array had changed color. Participants decided whether the cued square had the same color as the corresponding square in the first array or a different color.

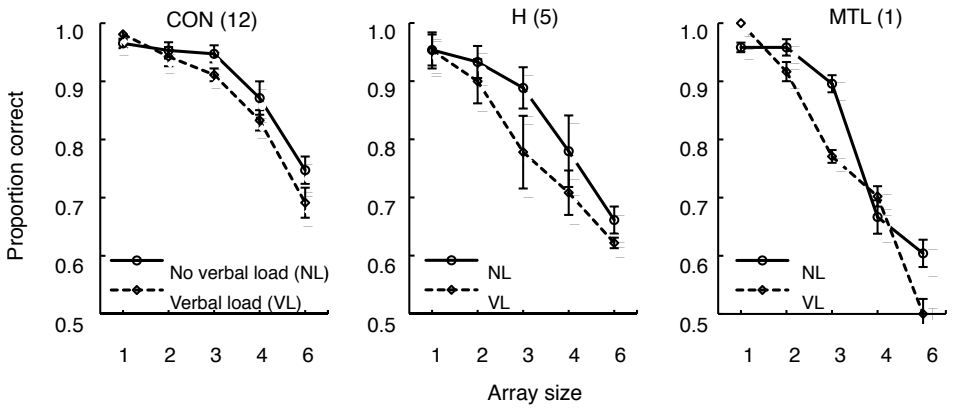

Figure 4.2. Performance as a function of array size with and without a verbal load. In the verbal load condition, participants were asked to hold two digits in memory during the trial. The data are averaged across all four delays (1s, 3s, 4s, 8s). CON = controls; H = patients with circumscribed hippocampal damage; MTL = patient GP with large medial temporal lobe lesions. Error bars indicate SEM.

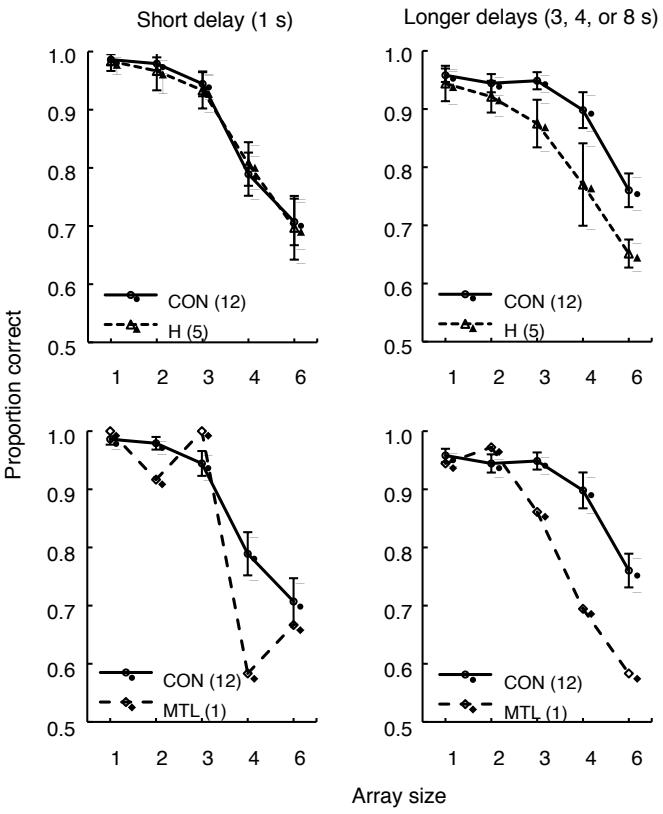

Figure 4.3. Performance as a function of array size (no verbal load). The data show performance at the 1-s delay (left panels) and at the three longer delays (right panels). Controls (CON) are compared to hippocampal patients (H; top panels) and to patient GP with large medial temporal lobe lesions (MTL; lower panels). Error bars indicate SEM.

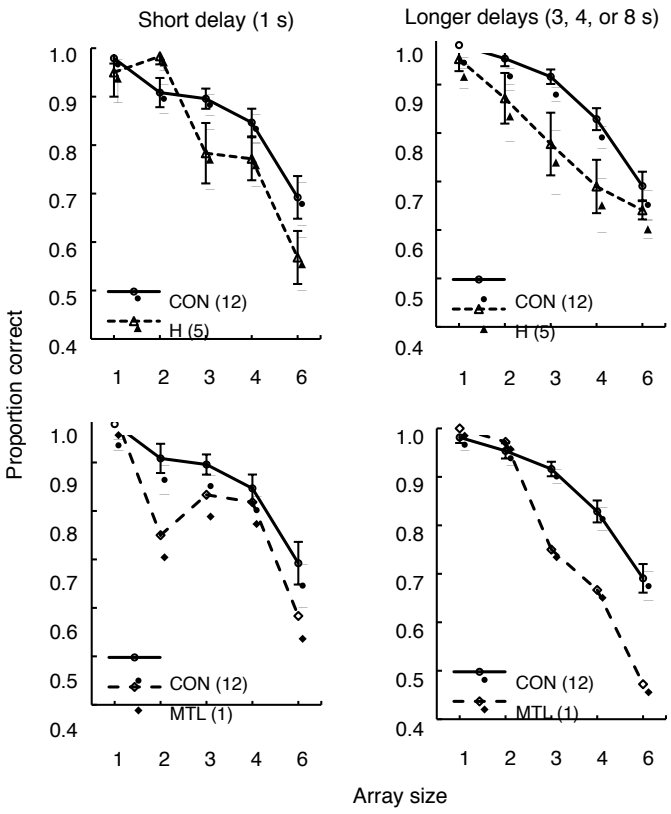

Figure 4.4. Performance as a function of array size (with a verbal load). The data show performance at the 1-s delay (left panels) and at the three longer delays (right panels). Controls (CON) are compared to hippocampal patients (H; top panels) and to patient GP with large medial temporal lobe lesions (MTL; lower panels). Error bars indicate SEM.

SUMMARY AND CONCLUSION

Recent neuropsychological and imaging literature has led to suggestions that the MTL may be important for working memory. This perspective challenges the historical view that these functions are independent of the MTL. Discussion of these ideas has often focused on a distinction between tasks with short retention intervals (a few seconds) and tasks with longer retention intervals. Yet, questions about the possible role of the MTL in immediate memory and working memory do not turn on any particular retention interval. Instead, the important distinction is between tasks where the material to be learned and maintained is within the capacity of immediate memory and working memory and tasks where what is to be learned exceeds capacity. When immediate memory capacity is exceeded, or when material must be retrieved following the redirection of attention, performance must depend on a stable memory store ("long-term memory") that permits the organization and retrieval of large amounts of information. Immediate memory and working memory, by contrast, deal "only with subspan memoranda, evanescently, as long as the subject's attention is directed towards the memorandum" (Drachman and Arbit 1966, p. 59).

A reappraisal of recent findings in light of these ideas (Chapter 1) suggests a parsimonious and consistent perspective by which to understand the patient data as well as the neuroimaging data. Many of the tasks that have been used make a significant demand on long-term memory. In tasks where working memory alone was sufficient to support performance, patients performed as well as controls regardless of

the kind of material to be held in mind. This pattern of performance was also observed in all three studies described in Chapters 2, 3, and 4.

Experiments 1A and 1B (Chapter 2; Jeneson et al. 2010b) assessed the ability of four patients with MTL damage to maintain up to seven object-location associations across a 1-s retention interval. In both experiments, the patients performed similarly to controls when only a small number of object-location associations needed to be remembered, but they exhibited an abrupt decline in performance when as many as 3 to 4 object locations needed to be remembered. The marked discontinuity in patient performance as they moved from smaller to larger set sizes occurred at about the same set size that first produced errors in controls. Presumably, controls began making errors at this point because the material now exceeded their working memory capacity.

Experiments 2A and 2B (Chapter 3; Jeneson et al. 2011b) assessed the ability of five patients with hippocampal lesions to retain object-in-scene information. The experiments differed in their demands on memory but assessed retention of the same information. In the first experiment, which used a continuous recognition format, participants needed to try to hold up to 9 scenes in mind, even when no scene intervened between the study scene and the corresponding test scene. Patients were impaired in this condition. In the second experiment, which used a conventional study-test format, participants needed to hold in mind only one scene at a time for either 3 s or 14 s. If maintenance of object-in-scene information is critically dependent on the hippocampus, one would expect hippocampal damage to impair

performance at the 3-s retention interval as well as at the 14-s retention interval. Instead, the patients exhibited fully intact memory for object-in-scene information when the retention delay was short (3 s), and they exhibited impaired memory when the delay was long (14 s).

Experiment 3 (Chapter 4; Jeneson et al., *submitted*) assessed the ability of five hippocampal patients and one patient with larger MTL lesions to maintain arrays of 1, 2, 3, 4, or 6 colored squares across delays of 1, 3, 4, or 8 s. At the 1s delay typically used to assess visual working memory capacity, the patients performed as well as controls at all array sizes. Their corresponding capacity estimates (Cowan's K) were also similar, and similar to those obtained in other studies (2 – 2.5 items for older adults). At the longer delays, the patients performed as well as controls at array sizes below the capacity limit (1 or 2 items), and they performed worse than controls only at array sizes that exceeded the capacity limit (3, 4, or 6 items).

The pattern of results observed in these experiments supports the idea that maintenance of visual or relational information in working memory is intact after damage to the hippocampus and related MTL structures and that damage to these structures impairs performance only when the task depends, in part, on long-term memory. The story that emerges is not that some kinds of working memory depend on the MTL, but rather that some kinds of short-delay tasks depend on long-term memory.

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SUPPLEMENTAL MATERIAL

Supplemental Table S1: Characteristics of memory-impaired patients

Patient (Gender)	Age (years)	Education (years)	WAIS-III IQ	WMS-R				
				Attention	Verbal	Visual	General	Delay
GP (M)	61	16	98	102	79	62	66	50
KE (M)	67	13.5	108	114	64	84	72	55
LJ (F)	71	12	101	105	83	60	69	<50
GW (M)	49	12	108	105	67	86	70	<50
JRW (M)	45	12	90	87	65	95	70	<50
RS (M)	52	12	99	99	85	81	82	<50

Notes:
WAIS-III is the Wechsler Adult Intelligence Scale-III and the WMS-R is the Wechsler Memory Scale-Revised. The WMS-R does not provide numerical scores for individuals who score < 50. IQ scores for JRW and RS are from the WAIS-R.

Patients GP, GW, LJ, and KE participated in Experiments 1A and 1B (Chapter 2). Patients GP, GW, JRW, LJ, KE, and RS participated in Experiments 2A and 2B (Chapter 3). All six patients participated in Experiment 3 (Chapter 4).

Supplemental Figure S1

Series of T1-weighted coronal images for GP, for each of the five patients with limited hippocampal lesions (KE, LJ, RS, GW, and JRW), and one control. The sections proceed in 7-mm intervals from the temporopolar cortex in the top section (with the exception of GW, whose top section is at the level of the perirhinal cortex) caudally through the splenium of the corpus callosum in the bottom section. The left side of the brain is on the right side of each image.

As described by Insausti et al. (1998) temporopolar cortex (TP) extends medially from the inferotemporal sulcus to the fundus of the temporopolar sulcus. Temporopolar cortex extends rostrally from the tip of the temporal pole caudally to the limen insula (LI), which approximates the border between the temporopolar cortex and perirhinal cortex. Caudal to temporopolar cortex, the collateral sulcus (CS) is the most important structure for the identification of medial temporal lobe cortices. At its most rostral extent, the collateral sulcus is surrounded entirely by perirhinal cortex (PR). Caudally, entorhinal cortex (EC) extends from the midpoint of the medial bank of the collateral sulcus to the subiculum, whereas perirhinal cortex extends laterally from the midpoint of the medial bank of the collateral sulcus to the inferotemporal cortex. Two millimeters caudal to the disappearance of the gyrus intralimbicus of the hippocampus (H), the collateral sulcus is surrounded by parahippocampal cortex (PH). The splenium of the corpus callosum approximates the posterior border of the parahippocampal cortex with the anterior occipital cortex.

The top section (1) shows the temporopolar cortex. Note that the portion of the temporal lobe missing in GP corresponds to temporopolar cortex and involves the lateral temporal lobe to a minimal extent (≈10%). None of the hippocampal patients has damage evident at this level. For LJ, only the tip of the temporal pole is visible at this level. For GW, the perirhinal cortex, not the more rostral temporopolar cortex, appears in this section.

The second section (2) shows the perirhinal cortex surrounding the collateral sulcus and the limen insula, which is the region where the cortex of the insula is continuous with the inferior cortex of the frontal lobe. The limen insula is evident only on the right side in the control brain and in GW and on the left side in JRW. In the other brains it appears caudal to this section. The third section (3) shows the collateral sulcus and surrounding perirhinal and entorhinal cortices. For GP, no collateral sulcus or surrounding tissue is evident. The fourth section (4) shows the anterior hippocampus and the adjacent perirhinal and entorhinal cortices. The hippocampus is absent bilaterally in GP, and no collateral sulcus or surrounding tissue is evident. GW has extensive damage to the hippocampus at this level. JRW has damage to the hippocampus on the left. KE's hippocampal damage is not evident at this level, but small bilateral lesions in the basal ganglia secondary to toxic shock syndrome are apparent. The lateral temporal lobe appears normal in all cases, and its volume is always within 1.2 standard deviations of the volume of the control mean.

The fifth section (5) shows the hippocampus and the adjacent perirhinal and entorhinal cortices. GP has no medial temporal lobe tissue at this level. Extensive hippocampal damage is evident at this level in KE, RS, GW, and JRW. The collateral sulcus and the surrounding perirhinal and entorhinal cortices appear normal in all of the hippocampal patients.

The sixth section (6) shows perirhinal cortex on the lateral bank of the collateral sulcus, near the perirhinal/parahippocampal cortex border. No medial temporal lobe tissue is evident in GP at this level. Also at this level, damage is evident in the hippocampal region of all of the hippocampal patients. Normal- appearing perirhinal cortex is evident in LJ and RS, and normal-appearing parahippocampal cortex is evident in GW. In JRW, normal perirhinal cortex is evident on the right side, and normal parahippocampal cortex is evident on the left. For KE, the cortex adjacent to the hippocampus (near the perirhinal/parahippocampal cortex border) also appears to be normal.

The seventh section (7) shows the hippocampus and the collateral sulcus, surrounded by parahippocampal cortex. GP has little normal medial temporal lobe tissue in either hemisphere. In addition, the patients have moderate damage to the hippocampus at this level (more severe damage in JRW), but the parahippocampal cortex appears entirely normal. The warping artifact in the right lateral temporal lobe of GW on this section, as well as on sections 8 and 9, does not interfere with the

assessment of his damage. The eighth section (8) also shows the hippocampus and the parahippocampal cortex surrounding the collateral sulcus. GP has some spared parahippocampal cortex at this level on the right side. For LJ and KE, moderate hippocampal damage is evident at this level. The collateral sulcus and surrounding parahippocampal cortex appear normal in all of the hippocampal patients.

The ninth section (9) shows the splenium of the corpus callosum, which defines the caudal border of parahippocampal cortex. At this posterior level, parahippocampal cortex is evident in all patients. For GP, volume reductions were not recorded at this level, but some sulcal widening is apparent. The hippocampus is evident at this level only in LJ, and it appears normal.