# Memory for Relations in the Short Term and the Long Term after Medial Temporal Lobe Damage

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**ABSTRACT: A central idea about the organization of declarative memory and the function of the hippocampus is that the hippocampus provides for the coding of relationships between items. A question arises whether this idea refers to the process of forming long-term memory or whether, as some studies have suggested, memory for relations might depend on the hippocampus even at short retention intervals and even when the task falls within the province of short-term (working) memory. The latter formulation appears to place the operation of relational memory into conflict with the idea that working memory is independent of medial temporal lobe (MTL) structures. In this report, the concepts of relational memory and working memory are discussed in the light of a simple demonstration experiment. Patients with MTL lesions successfully learned and recalled two word pairs when tested directly after learning but failed altogether when tested after a delay. The results do not contradict the idea that the hippocampus has a fundamental role in relational memory. However, there is a need for further elaboration and specification of the idea in order to explain why patients with MTL lesions can establish relational memory in the short term but not in long-term memory. © 2017 Wiley Periodicals, Inc.**

**KEY WORDS: hippocampus; amnesia; relational memory**

## INTRODUCTION

Declarative memory refers to the capacity to retrieve facts and events as conscious recollections (Squire, 1982; Cohen, 1984). This capacity depends on the integrity of the hippocampus and related medial temporal lobe (MTL) structures (Squire and Zola, 1991; Eichenbaum and Cohen, 2001). One important principle governing the function of the MTL is the distinction between short-term (or working) memory and long-term memory. Working memory refers to the ability to temporarily maintain a limited amount of information in mind through sustained attention (Baddeley and Hitch, 1974). Long-term memory allows for retrieval from the past when information no longer occupies the current stream of thought, either because working memory capacity has been exceeded or because attention has been diverted. Studies of memory-impaired patients with MTL damage have typically found working memory to be intact, despite impaired long-term memory (Drachman and Arbit, 1966; Baddeley and Warrington, 1970; Baddeley et al., 2011; Jeneson and Squire, 2012). Note that the retention interval is not the key factor that determines whether patients succeed or fail at memory tests. The important factors are the capacity of working memory and the effect of attention, i.e., the amount of material that can be held in mind and how successfully it can be attended to and rehearsed. Indeed, the earliest treatments of short-term and long-term memory did not favor any particular retention interval (James, 1890; Drachman and Arbit, 1966). This does not mean that the retention interval is irrelevant to understanding patient performance. The probability that attention will be diverted (and information lost from working memory) increases with time after learning. As a result, as time passes the contribution of long-term memory to performance becomes correspondingly more important.

Another important idea about the organization of declarative memory is that it provides for the coding of relationships between items (Eichenbaum et al., 1991). Specifically, declarative memory is supported by relational representations that permit comparison and contrast among items and contexts. For example, in the case of a study list that includes the item "fork", the experimenter is not later asking: "Have you ever seen a fork before?" Rather the question is whether the item can be recognized as having appeared on the study list and, thus, whether a relationship has been established between the test item and the recent study episode. This proposal about relational memory has typically referred to the operation of long-term memory. However, some studies have raised the possibility that memory for relations might depend on the MTL even at short retention intervals and perhaps even when the task falls within the province of short-term (or working) memory (Hannula et al., 2006; Olson et al., 2006; Yee et al., 2014; Koen et al., 2017). For example, ". . .the memory functions of the hippocampus [might] have less to do with any distinction between long-term and short-term (or working) memory than it has to do with the distinction between relational memory and memory for items" (Hannula et al., 2006, p. 8358).

This article was published online on 21 February 2017. After online publication, minor revisions were made to the text. This notice is included in the online and print versions to indicate that both have been corrected on 28 February 2017.

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Conflicts of interest: The author declares no conflict of interest.
Accepted for publication 7 February 2017.
DOI 10.1002/hipo.22716
Published online 11 February 2017 in Wiley Online Library (wileyonlinelibrary.com).

This formulation appears to place the operation of relational memory into conflict with the idea that short-term (or working) memory is independent of MTL function. The question is whether the formation of associations and relationships is critically dependent on the hippocampus, independently of whether a task can be supported by working memory. Or is the hippocampus principally involved in the formation of long-term, declarative memory with relational representations developing as part of this process? Two recent studies of the developmental amnesic patient Jon found intact performance in a series of relational working memory tasks (Baddeley et al., 2010, 2011). Other studies of MTL patients found intact performance for object-place associations when testing occurred shortly after learning (Shrager et al., 2008; Jeneson et al., 2010; Jeneson and Squire, 2012). Thus, working memory can apparently support some tasks of relational memory independently of the hippocampus. Yet, there is often ambiguity about whether a task can be managed entirely by working memory, and it would be useful to have a simpler test that affords a sharper contrast between conditions that test working memory and conditions that test long-term memory.

The present study used a simple word-pair task, the quintessential example of relational learning, and asked participants to learn only two pairs of words. If the ability to establish relationships in memory is fundamental to hippocampal function, then MTL patients should have difficulty forming associations between words. Performance should be impaired even at short retention intervals, despite the fact that the task involves subspan material that is simple enough to be managed within working memory. In the study, patients with MTL lesions and controls learned two word pairs and then were tested directly after learning and after a 25-min delay.

## MATERIALS AND METHODS

### Participants

Five memory-impaired patients participated, four with bilateral lesions thought to be limited to the hippocampus (CA fields, dentate gyrus, and subicular complex) and one with larger medial temporal lobe lesions (Table 1). Patients G.W. and D.A. became amnesic in 2001 and 2011, respectively, following a drug overdose and associated respiratory failure. Patient K.E. became amnesic in 2004 after an episode of ischemia associated with kidney failure and toxic shock syndrome. Patient L.J. (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.

Estimates of medial temporal lobe damage were based on quantitative analysis of magnetic resonance (MR) images from 19 age-matched, healthy males for K.E., G.W., and G.P., 11 age-matched, healthy females for patient L.J. (Gold and Squire, 2005), and 8 younger healthy males for D.A. Patients K.E., G.W., L.J., and D.A. have an average bilateral reduction in hippocampal volume of 49, 48, 46, and 35%, respectively. All values are at least 2.9 SDs from the control mean. On the basis of two patients (L.M. and W.H.) with similar bilateral volume loss in the hippocampus for whom detailed postmortem neurohistological information was obtained (Rempel-Clower et al., 1996), the degree of volume loss in these four patients may reflect nearly complete loss of hippocampal neurons. Volume estimates for the parahippocampal gyrus include temporopolar, perirhinal, entorhinal, and parahippocampal cortices. K.E., G.W., L.J., and D.A. have an average bilateral reduction in the volume of parahippocampal gyrus of 11, 10, −17, and −5%, respectively (all values within 2 SDs of the control mean). The minus values indicate volumes that were larger for a patient than for controls. These values are based on published guidelines for identifying the boundaries of the parahippocampal gyrus (Insausti et al., 1998; Frankó et al., 2014).

One patient (G.P.) has severe memory impairment resulting from viral encephalitis in 1987. During repeated testing over many weeks he did not recognize that he had been tested before (Bayley et al., 2005). G.P. has an average bilateral reduction in hippocampal volume of 96%. The volume of the parahippocampal gyrus is reduced by 94%. Eight coronal magnetic resonance images from each patient, together with detailed descriptions of the lesions, can be found elsewhere (Knutson et al., 2013).

*TABLE 1.*

*Characteristics of Memory-Impaired Patients*

| | | | | WMS-R | | | | |
|---|---|---|---|---|---|---|---|---|
| Patient | Age (years) | Education (years) | WAIS-III IQ | Attention | Verbal | Visual | General | Delay |
| D.A. | 32 | 12 | 95 | 104 | 90 | 91 | 90 | 56 |
| K.E. | 75 | 13.5 | 108 | 114 | 64 | 84 | 72 | 55 |
| L.J. | 78 | 12 | 101 | 105 | 83 | 60 | 69 | <50 |
| G.W. | 56 | 12 | 108 | 105 | 67 | 86 | 70 | <50 |
| G.P. | 70 | 16 | 98 | 102 | 79 | 62 | 66 | 50 |

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

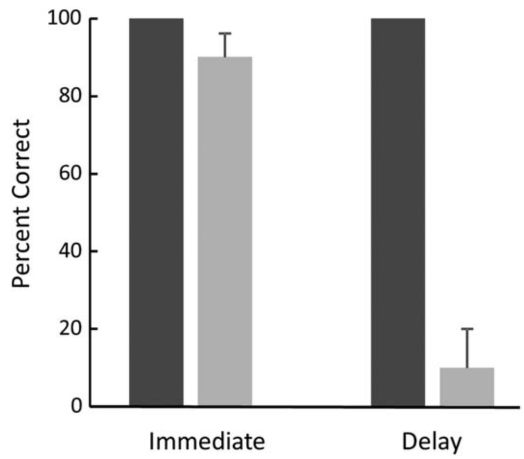


**FIGURE 1. Healthy volunteers (black bars, $n = 6$) and memory-impaired patients (gray bars, $n = 5$) saw two word pairs (5s/pair) in each of two test sessions. Then immediately afterwards, and again after 25 min, participants were shown the first word of each pair and tried to recall the second word. The scores are the mean for two separate test sessions. Brackets show standard error of the mean.**

Six healthy volunteers also participated (2 females, mean age = 67.7 years; mean education = 14.4 years). All procedures were approved by the Institutional Review Board at the University of California San Diego, and participants gave written informed consent prior to participation.

## Procedure

In each of two test sessions (mean interval between sessions = 90 days), participants were asked to learn and remember two unrelated word pairs (Session 1: Officer-Plant, King-Baby; Session 2: Cat-Garden, Stone-Ocean). They were told that they would see cards, each displaying two words and that they should remember the words that were paired together. They were not told how many pairs would be presented but were told that, afterward, they would see cards displaying one word and would be asked to recall the associated word. In each session, word pairs were displayed on a card one at a time while the experimenter read the pair aloud (5 s per word pair). Directly after both word pairs were presented, and again after a 25-min delay, the first word from each pair was displayed one at a time and in each case the experimenter asked: "What word went with Officer [or King, Cat, Stone]?" The word pairs were always tested in the order that they had originally been presented.

# RESULTS

Figure 1 shows the results. In both sessions, all control participants correctly recalled the two word pairs, both immediately after studying them and after 25 min. The patients scored 90.0 ± 6.1% correct immediately after studying the pairs (controls vs. patients, $P > 0.10$) and 10.0 ± 10% after 25 min (controls vs. patients, $P < .001$). For the immediate test, all the patients scored perfectly in the first test session. In the second test session, two patients failed to recall the first pair. For the delayed test, four of the five patients recalled none of the pairs in either test session. One patient (D.A.) successfully recalled the pairs after the delay in the first test session but failed to recall any pairs after the delay in the second test session. Notably, patient G.P., who has large medial temporal lobe lesions that include virtually all of the hippocampus bilaterally, recalled all the pairs in the immediate test and none of the pairs in the delay test.

# DISCUSSION

Patients with MTL lesions successfully recalled two word pairs when tested directly after learning but failed when tested after a 25-min delay. Thus, the patients were able to learn and recall relationships between items when the retention interval was brief. Three patients performed perfectly, and two patients missed one of the two pairs in the second test session. At the 25-min delay, four of the five patients failed all the tests, typically offering a word that was a strong associate of the cue word (e.g., Cat-Mouse). Patient D.A. (the youngest and least impaired of the group) correctly recalled both words after the delay in the first test session.

Note that if a patient could not encode relational information but could hold the individual words in working memory, then the expected score in response to a cue word at the immediate test would be 33% correct. That is, in the absence of any available relational information, a patient with knowledge of the individual words would need to choose among the other three words that were presented in the same test session. Accordingly, a score above 33% correct indicates that relational memory has been acquired. On the immediate test, three patients scored 100% correct and two patients scored 75% correct. After the delay, four of the patients scored 0% correct, and one scored 50% correct.

The study illustrates a condition in which MTL damage spares relational memory. In this instance, learning and memory of the relationships between words presumably succeeded because subspan material was used that could be held in mind for a brief period. Although MTL structures may be engaged at the moment of learning, they are not initially essential for performance in the case of subspan material, because for a time the information can be supported by representations in neocortex, i.e., by working memory (Postle, 2006; Fuster, 2015). The present study might seem too simple or even too frivolous to make this point, under the objection that participants could easily repeat the word pairs to themselves during the few seconds needed to bridge the retention interval. Yet, even the ability to rehearse the words in the same order that they were presented requires relational knowledge of which word came first and which came second. And the possibility of rehearsal (and holding in mind) is precisely what is afforded by the availability of working memory.

The present study provides a simple demonstration that the establishment of relational memory can be supported by working memory for a brief period, independently of a contribution from MTL structures. In contrast, the establishment of relational memory in the long term depends critically on the MTL. It remains possible of course that some form of associative (relational) memory will be found to depend on the hippocampus (or other MTL structures), even under conditions when the task can be managed within working memory. Nonetheless, a number of explicit tests of relational working memory have been carried out, and performance was intact after MTL lesions (Shrager et al., 2008; Jeneson et al., 2010; Baddeley et al., 2010; Baddeley et al., 2011; Jeneson and Squire, 2012). As suggested elsewhere (Baddeley et al., 2010; Jeneson and Squire, 2012; Squire and Dede, 2015), many earlier studies reporting impaired performance in MTL patients at short retention intervals appear to involve supraspan material (i.e., material that exceeds working memory capacity) and, accordingly, would place a significant demand on long-term memory. Indeed, word-pair learning itself can create difficulty for memory-impaired patients when testing occurs directly after learning, if the number of word pairs that are presented challenges working memory capacity. For example, in an early study involving 10 word pairs (Musen et al., 1990), eight patients recalled a mean of only 0.3 words immediately after presentation of the words pairs. Eight controls recalled 6.0 of the words.

In summary, the present data do not refute the idea that the hippocampus has a fundamental role in relational memory. However, the results do suggest the need for further elaboration and specification of the idea to explain why patients with MTL lesions can establish relational memory in the short term but not in long-term memory. Finally, quite apart from the concept of relational memory, the present data draw attention to the historic distinction between short-term (working) memory and long-term memory as a central feature of brain organization that is fundamental to the structure of memory.

## Acknowledgments

I thank Jennifer Frascino for assistance and Christine Smith and John Wixted for helpful comments. Supported by the Medical Research Service of the Department of Veterans Affairs (5101CX000359) and NIMH (24600).

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