UNIVERSITY OF CALIFORNIA, SAN DIEGO

# Encoding, Remembering, Imagining and Medial Temporal Lobe Function

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

in

Psychology

by

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2016

The Dissertation of Adam J. Dede is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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2016

# DEDICATION

To the bureaucrats whose jobs depend on this exercise in formatting and paperwork

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ACKNOWLEDGEMENTS

The work reported here would have been impossible alone. I would like to thank my advisors, Larry Squire and John Wixted. Their advice and encouragement has been invaluable. I have been lucky to learn from them. I would also like to thank Christine Smith for discussing wide ranging topics about memory and acting as a third mentor, Jennifer Frascino for running subjects and helping with experimental design, and Sherry Hargrove for keeping the administrative side of the lab running smoothly.

Many thanks all of the people who helped me with data analysis: Ryan Ward, Meilinne Hancock, Soyun Kim, Reina Mizrahi, and Katherine Ann.

Chapter 1, in full, is a reprint of the material as it appears in “Hippocampal damage impairs recognition memory broadly, affecting both parameters in two prominent models of memory” in PNAS: USA 110(16):6577-82. Dede, AJO, Wixted, JT, Hopkins RO, Squire, LR, 2013. The dissertation author was the primary investigator and author of this paper.

Chapter 2, in full, has been submitted for publication of the material as it may appear in PNAS: USA by Dede, AJO, Frascino, JC, Wixted, JT, Squire, LR. The dissertation author was the primary investigator and author of this paper.

Chapter 3, in full, has been submitted for publication of the material as it may appear in PNAS: USA by Dede, AJO, Wixted, JT, Hopkins RO, Squire, LR. The dissertation author was the primary investigator and author of this paper.

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### Publications

Dede, A.J.O., Wixted, J.T., Squire, L.R. (Submitted). Learning and remembering real-world events after medial temporal lobe damage.

Dede, A.J.O., Wixted, J.T., Hopkins, R.O., Squire, L.R. (submitted). Autobiographical memory, future imagining, and the medial temporal lobe.

Kim, S., Dede, A.J.O., Hopkins, R.O., Squire, L.R. (2015). Memory, scene construction, and the human hippocampus. PNAS: USA.

Squire, L.R., Dede, A.J.O. (2015). Conscious and unconscious memory systems. Cold Spring Harb. Perspect. Biol. 1-14.

Dede, A.J.O., Squire, L.R., Wixted, J.T. (2014). A novel approach to an old problem: Analysis of systematic errors in two models of recognition memory. Neuropsychologia, 52; 51-56.

Dede, A.J.O., Wixted, J.R., Hopkins, R.O., Squire, L.R. (2013). Hippocampal damage impairs recognition memory broadly, affecting both parameters in two prominent models of memory. PNAS: USA, 110; 6577-6582.

### Abstracts and Conference Presentations

Dede, A.J.O., Hopkins, R.O., Squire, L.R. (2015). Temporal features of narrative construction are different for healthy older adults and patients with hippocampal damage. Poster presented at the annual meeting of the Society for Neurosciece in Chicago.

Kim, S., Dede, A.J.O., Hopkins, R.O., Squire, L.R. (2014). Intact boundary extension in memory-impaired patients with hippocampal lesions. Poster

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Dede, A.J.O., Hopkins, R.O., Squire, L.R. (2014). The impact of anterograde amnesia on narrative construction of past and future episodes. Poster presented at the annual meeting of the Society for Neuroscience in Washington D.C.

Dede, A.J.O., Squire, L.R., Wixted, J.T. (2013). The dual process signal detection model makes systematic errors. Poster presented at the annual meeting of the Society for Neuroscience in San Diego, CA.

Dede, A.J.O., Wixted, J.T., Hopkins, R.O., Squire, L.R. (2013). Systematic error in the dual process signal detection model of recognition memory. Poster presented at the annual meeting of the Cognitive Neuroscience Society in San Francisco, CA.

Dede, A.J.O., Hopkins, R.O., Wixted, J.T., Squire, L.R. (2012) Hippocampal damage impairs recognition memory broadly, affecting both parameters of interest in two prominent models of recognition memory. Poster presented at the annual meeting of the Society for Neuroscience in New Orleans, LA.

Dede, A.J.O., & Wixted, J.T. (2012). Confidence accumulation or variable criteria? How biasing can affect zROC slopes. Poster presented at the annual meeting of the Psychonomic Society, Minneapolis, Mn.

Dede, A.J.O., & Arndt, J. (2012). Recollection and familiarity sum together: Evidence from ERP. Poster presented at the annual meeting of the Cognitive Neuroscience Society. Chicago, IL.

Shasha, C., Hommel, N., Dede, A.J.O., Whitaker, E., Corbett, K., & Arndt, J. (2011). The role of associations in producing false memories. Poster presented at the annual meeting of the Eastern Psychological Association. Cambridge, MA.

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Dede, A.J.O., Shasha, C., Dorot, S., Corbett, K., & Arndt, J. (2010). Association directionality and false recognition. Poster presented at the annual meeting of the Psychonomic Society, St. Louis, MO.

Bennion, K., Dede, A.J.O., Shasha, C., Dorot, S., Guillet, R., & Arndt, J. (2009). The impact of emotion on item and associative recognition. Poster presented at the annual meeting of the Psychonomic Society, Boston, MA.

ABSTRACT OF THE DISSERTATION

Encoding, Remembering, Imagining and Medial Temporal Lobe Function

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Doctor of Philosophy in Psychology

University of California, San Diego, 2016

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The hippocampus and related medial temporal lobe (MTL) structures are known to be important for declarative memory. Yet, their precise role remains unclear. In three studies, we sought to characterize the role of the hippocampus in encoding, remembering, and imagining. The first study assessed the role of

the hippocampus in encoding and remembering memories for words encountered in a laboratory setting. The second study assessed the role of the hippocampus in encoding and remembering real- world events. The third study assessed the role of the hippocampus in remembering natural autobiographical memories and imagining future episodes. We conclude that the hippocampus plays a broad role in declarative memory, functioning to encode information whenever the capacity of working memory is surpassed.

# INTRODUCTION

Declarative memory is the part of memory referred to when the term "memory" is used in everyday language. We are consciously aware of it, and we call upon it to interpret the events of our lives. It is widely agreed that structures within the medial temporal lobe (MTL) of the brain are important for declarative memory. These structures are the hippocampus and the adjacent perirhinal, entorhinal, and parahippocampal corticies. However, the precise role of the hippocampus and adjacent structures remains unclear.

Two patterns of performance are often observed in patients with damage limited to the hippocampus. First, these patients are impaired on laboratory tasks of memory for all types of stimuli (e.g., words, pictures, smells) and under various retrieval conditions (e.g., recognition and recall). Second, when patients with hippocampal damage are asked to retrieve memories from their past, they are impaired at remembering information acquired shortly before the onset of memory-impairment, but their ability to retrieve information acquired long before the onset of memory-impairment is relatively spared. The later observation is much debated. At issue is whether patients with hippocampal damage can retrieve remote memories that have all the characteristics of those retrieved by healthy individuals.

It has been suggested that the hippocampus may be particularly important for laying down and retrieving memories involving a certain type of information. According to one view, the hippocampus is important for the experiential aspects

of memory (termed episodic memory) but not for the factual aspects of memory (termed semantic memory). According to another view, the hippocampus is important for spatial processing. A third view holds that the hippocampus is important for all aspects of declarative memory. According to this view, seemingly specific deficits may sometimes result when the amount of information needed to perform a task exceeds the capacity which may be held online in working memory.

Here, three studies are presented in three chapters. The same group of memory-impaired patients with damage limited to the hippocampus participated in all three studies. Chapter 1 presents a study of recognition memory in which computational modeling was used to assess memory function. Specifically, two prominent models of memory were fit to the data collected from patients and matched controls. Both models provide two parameters of memory performance. Each parameter is sensitive to a different aspect of memory performance. At issue was whether hippocampal damage resulted in a broad impairment affecting both parameters in both models or a specific impairment affecting only one parameter in each model. If only one parameter were affected, then it might suggest that the hippocampus is relatively more important for some types of declarative memory than others. Results indicated that both parameters were affected in both models.

Chapter 2 presents a prospective study of autobiographical memory for real-world events. Patients and controls were taken individually on a walk around the University campus during which 11 planned events occurred. Upon returning

to the laboratory, participants' memory was tested for the events of the walk. At issue was whether hippocampal damage resulted in a broad impairment affecting memory for all aspects of the walk or a specific impairment affecting memory for only particular aspects of the walk. Results indicated that for local information about individual events, patients exhibited equivalent impairment for all types of content. By contrast, patients were strikingly impaired for global information about the relationships between events.

Chapter 3 presents a study of autobiographical memory retrieval and future imagining. Patients and matched controls were asked to retrieve specific events from the near and distant past and to imagine events in the near and distant future. Neuroimaging has revealed that the same set of brain regions including the hippocampus is active during both past remembering and future imagining. Thus, it was of interest to know whether patients with hippocampal damage could imagine the future. At issue was whether patients would be able to construct narratives containing content of similar quality and quantity as those constructed by controls. Results indicated that patients were impaired at remembering the near past, which required recall of events from after the onset of memory impairment, but they were able to recall events from the distant past and to imagine events in the future. Further, comparison of our patients to those of another study revealed that divergent findings between studies are likely linked to differences in the locus and extent of brain damage.

# CHAPTER 1

## Hippocampal damage impairs recognition memory broadly, affecting both parameters in two prominent models of memory

Declarative memory is thought to rely on two processes: recollection and familiarity. Recollection involves remembering specific details about the episode in which an item was encountered, and familiarity involves simply knowing that an item was presented even when no information can be recalled about the episode itself. There has been debate whether the hippocampus supports only recollection or whether it supports both processes. We approached this issue in a relatively theory-neutral way by fitting two prominent models that have been used to describe recognition memory: dual process signal detection (DPSD) and unequal variance signal detection (UVSD). Both models yield two parameters of interest when fit to recognition memory data. The DPSD model yields estimates of recollection (r) and familiarity (d'). The UVSD model yield estimates of the ratio of the variance of target and foil memory strength distributions ($\sigma_{target}/\sigma_{foil}$) and the difference in the means of the two distributions (d). We asked how the two parameters of each model were affected by hippocampal damage. We tested five patients with well-characterized bilateral lesions thought to be limited to the hippocampus and age-matched controls. The patients exhibited a broad memory deficit that markedly reduced the value of both parameters in both models. In addition, the pattern of results exhibited by the patients was recapitulated in

healthy controls as the delay between learning and testing was extended. Thus, hippocampal damage impairs both component processes of recognition memory.

## Introduction

The formation of declarative memory depends on the integrity of the hippocampus and related medial temporal lobe structures (MTL; 1). A widely studied example of declarative memory is recognition memory, the ability to correctly judge that an item was encountered previously. Recognition memory is thought to consist of two component processes, recollection and familiarity (2, for review see 3). Recollection involves recalling specific details about the episode in which an item was encountered. Familiarity involves simply knowing that an item was presented without remembering anything about the episode itself. While the hippocampus and other MTL structures are important for recognition memory (4), their relative importance for recollection and familiarity is unclear. One view is that the hippocampus is important for recollection, but is entirely uninvolved in familiarity (for review see 5). A second view is that the hippocampus contributes to both processes (for review see 6). We focus here on two models that have been used to characterize the memory impairment associated with hippocampal lesions: the dual process signal detection (DPSD) model (DPSD; 7, 8) and the unequal variance signal detection (UVSD) model (UVSD; 9, 10). These models are typically fit to experimental data from recognition memory tests in which participants use a confidence rating scale to discriminate targets that appeared on a prior study list from foils that did not. Both models yield two parameters of

interest. For the DPSD model, the two parameters consist of the proportion of targets that theoretically achieve a qualitatively distinct state of memory such that they are recognized with high confidence and high accuracy; and d', the quantitative difference between the average memory strength of targets and the average memory strength of foils, divided by the standard deviation of the two distributions (which is assumed to be identical). These two parameters have been termed recollection (r) and familiarity (d'), because the parameter values are assumed to correspond directly to the strength of these two processes.

For the UVSD model, the two parameters consist of $\sigma_{target}/\sigma_{foil}$, the ratio of the standard deviations of memory strengths associated with targets and foils, and d, the quantitative difference between the average memory strength of targets and the average memory strength of foils, divided by the standard deviation of the foil distribution. In the UVSD model, these two parameters capture distinct quantitative properties of the memory signal but are neutral with respect to the constructs of recollection and familiarity.

Although the DPSD and UVSD models do not provide the same theoretical interpretation of recognition memory performance, the two parameters in each model may nevertheless capture similar trends in the data. Thus, it is of interest to know whether hippocampal lesions affect one parameter of each model (consistent with a selective memory impairment) or both parameters of both models (consistent with a broad memory impairment). Previous research using a model-based approach to understanding the effect of hippocampal lesions has yielded inconsistent results. The present study sought to clarify the

role of the hippocampus in recognition memory using a relatively theory-neutral approach to determine (according to each model) whether only one parameter or both parameters were affected. We also address methodological issues that may have contributed to the conflicting findings in earlier studies.

## Results

### *Experiment 1*

Experiment 1 tested the recognition performance of patients with damage limited to the hippocampus and a matched group of healthy volunteers using 50-item word lists and a 3-5 minute retention interval. Analysis was performed at the individual subject level.

One control was eliminated because both his DPSD recollection and UVSD $\sigma_{target}/\sigma_{foil}$ estimates were greater than 3 standard deviations below the means of the other estimates for these parameters. The remaining 11 controls performed better than the patients (83% vs. 65% correct; $t(14) = 4.5$, $p<.01$). Both groups performed well above chance ($ps<.01$; see Table 2 for hit and false alarm rates). In addition, the two groups adopted a similar response criterion (bias) (for patients $\beta=1.06$; for controls $\beta=1.00$).

For the DPSD model, both parameter estimates of interest were lower for the patients than for the controls (Figure 1). Estimates of familiarity were .70 and 1.78, respectively ($t[14]=4.27$, $p<.01$). Estimates of recollection were .03 and .22, respectively ($t[10.4]=3.04$, $p=.01$; unequal variance t-test). The two parameters associated with the UVSD model were also reduced (Figure 1). Estimates of d were .75 and 2.35 for patients and controls, respectively ($t[14]=4.90$, $p<.01$).

Estimates of $\sigma_{target}/\sigma_{foil}$ were 1.09 and 1.23, respectively ($t[13.3]=2.31$, $p=.04$; unequal variance t-test) .

The parameter estimates from the two models indicated that declarative memory was broadly impaired in the patients. To test whether the parameters of the two models capture the same empirical trends in the data, we computed correlations between the corresponding parameters across participants. The familiarity estimate from the DPSD model and the d estimate from the UVSD model correspond to each other in the sense that they both determine the degree to which the curvilinear Receiver Operating Characteristic bows away from the diagonal line (7). These parameters were strongly correlated for both the patients and the controls ($r[3]=.97$ and $r[9]=.77$, respectively; $ps<.01$). The recollection and $\sigma_{target}/\sigma_{foil}$ parameters were also correlated in the patient group but not in the control group ($r[3]=.93$ and $r[9]=.11$, respectively; $p=.02$ and .74, respectively).

Finally, the goodness of fit of the two models to the data was assessed for each participant using a $\chi^2$ test. Thus the frequency of responses at each confidence level (1 to 6) predicted by the two models was compared to the frequency of responses that was observed. The UVSD model outperformed the DPSD model for 7 of the 11 controls and for 4 of the 5 patients.

*Experiment 2*

Experiments 2 and 3 were designed to assess whether the pattern of performance exhibited by the patient group in Experiment 1 would be

recapitulated in controls when their performance matched patient performance. Experiment 2 just characterized memory in controls as a function of increasing retention interval. This procedure identified retention intervals (1 day and 7 days) at which control performance approximated the performance of the patients. In Experiment 3, sufficient data were collected at these two retention intervals for analysis at the individual subject level. In this way, it was possible to compare directly the data collected from patients in Experiment 1 to data from controls with matched memory performance.

Accuracy, hit rate, and false alarm rate data are presented in Table 3. For the DPSD model, estimates of both familiarity and recollection decreased monotonically with delay (Figure 2, filled symbols). Note that the recollection estimate (Figure 2B) decreased more rapidly than the familiarity estimate, reaching a score of zero after only 1 day. For the UVSD model, estimates of both d and $\sigma_{target}/\sigma_{foil}$ also decreased monotonically (Figure 2, open symbols).

The $\sigma_{target}/\sigma_{foil}$ estimate decreased more rapidly than the d estimate, approaching the minimum value of 1.0 after 1 day.

Based on group $\chi^2$ values, the UVSD model fit the data better than the DPSD model at all 5 delays.

*Experiment 3*

Controls tested after a 1-day delay performed similarly to, albeit a little better than, the patients in Experiment 1, who were tested after a 3-5 minute delay (Figure 3). Controls tested after a 7-day delay also performed similarly to,

but a little worse than, the patients in Experiment 1. The 1-day controls scored 71% correct, the patients in Experiment 1 scored 65% correct, and the

7-day controls scored 58% correct. Hit and false alarm rate data for all groups are presented in Table 4. There were no significant differences between the model parameter estimates for the patients and either group of controls (1-day and 7-day; ps>.05).

Correlation analyses between corresponding parameters of the DPSD and UVSD models across individual participants again indicated that the two models described similar trends in the data. Discriminability estimates of the two models were significantly correlated in the 7-day group (familiarity and d; r[5]=.93, p<.01) and marginally correlated in the 1-day group (r[3]=.85, p=.07). Estimates of $\sigma_{target}/\sigma_{foil}$ and recollection fell short of significance in both the 1- day (r[3]=.83, p=.08), and 7-day (r[5]=.65, p=.11) conditions.

Based on individual $\chi^2$ values, the UVSD model provided a better fit to the data than did the DPSD model for 3 of the 5 controls in the 1-day group and 6 of the 7 controls in the 7-day group.

## Discussion

Patients with bilateral damage to the hippocampus exhibited a broad deficit in recognition memory, as indicated by a reduction in the two key parameter estimates of two prominent models, DPSD and UVSD (Experiment 1). In addition, the parameter estimates of both models were reduced for healthy volunteers as memory became weaker during normal forgetting (Experiment 2).

Finally, according to both models, the performance of the patients was similar to the performance of healthy volunteers, when their memory was made weaker by extending the retention interval (Experiment 3).

Taken together, the results indicate that the performance of patients differed quantitatively, but not qualitatively, from that of controls. Thus, to the extent that the two parameters of the DPSD and UVSD models are differentially sensitive to the processes of recollection and familiarity (an explicit assumption of the DPSD model), the results suggest that damage limited to the hippocampus impairs both recollection and familiarity.

It is of interest to know whether one parameter of either model was affected by hippocampal damage more than the other parameter of the same model. However, it is difficult to make this determination when comparing a probability estimate, on the one hand, and a discriminability estimate on the other. According to the DPSD model, the recollection parameter decreased by 86% and the familiarity parameter decreased by 61%. According to the UVSD model, the corresponding decreases were 68% and 61%. Our main point is that both parameters of both models were affected by hippocampal lesions, a finding that counts against the view that familiarity is preserved after hippocampal lesions (5).

Three studies have used the DPSD model, or both models, to characterize the memory impairment of patients with damage thought to be limited to the hippocampus (11-14). Yonelinas et al. (12) reported that the performance of patients reflected a selective decrease in the recollection parameter of the DPSD

model. Aggleton et al. (14) reached a similar conclusion for patient KN. By contrast, Wais et al. (13) found that hippocampal damage affected both the recollection and familiarity parameters of the DPSD model as well as both parameters of the UVSD model.

The study by Wais et al. (13) differed from the two other studies in two important respects. First, the analyses that were based on the DPSD and UVSD models were applied only to group data and not to individual subject data. Second, short study lists were used. When group data are analyzed, averaging artifacts can yield parameter estimates that are not representative of individual performance (15, 16). In addition, it has been suggested that with short lists patients might rely on working memory to maintain and then recollect words from the study list (17). If so, patient performance should not be taken as evidence for successful retrieval from long-term memory. The current study shows that these factors were not responsible for the broad memory impairment reported earlier (13). First, in the present study, the critical analyses were performed at the level of the individual participant and did not depend on group data. Second, long study lists were used in all conditions.

We next consider the two studies that reported a selective impairment in recollection after hippocampal damage (12, 14). In the first study (12) the DPSD model was fit to data from four patients thought to have damage limited to the hippocampus based on the fact that their amnesia resulted from a period of hypoxia after cardiac arrest. MR images were not available. Compared to the parameter estimates from a matched control group, the recollection estimate

derived for the patients was significantly reduced. The familiarity estimate was also reduced, but not significantly. However, in the analysis, as reported, data from deep and shallow encoding conditions were combined and then analyzed as though the data had been drawn from a single memory strength condition. When items from different strength conditions are intermixed, the result is a non-Gaussian mixture distribution. Under these conditions, the use of Gaussian-based signal detection models (such as the DPSD and UVSD models) are not appropriate (18). Thus, no conclusions can be drawn based on a fit of the DPSD model to these data.

In the second study (14), patient KN was described as having a selective recollection deficit. However, KN had intact recognition memory scores as measured by both percent correct (KN = 72%, controls = 73%) and $d_a$ (KN = 1.29, controls = 1.35). Furthermore, according to the DPSD model, neither KN's recollection z-score (-1.14) nor his familiarity z-score (+.34) differed by more than 1.2 standard deviations from the mean of the controls. It was proposed that patient KN's memory impairment was obscured by the unusually poor performance of one control, whose recollection z-score was more than 3 standard deviations below the control mean. When that outlier was excluded, the DPSD recollection z-score for patient KN became -2.16 (suggesting an impairment). However, the corresponding DPSD familiarity score without the outlier was not reported, so that one cannot determine whether KN's memory impairment was selective for recollection.

The question naturally arises whether differences in results between

patient groups might reflect differences in the locus and extent of damage. For example, it has been proposed that two of the patients whom we have studied likely have damage outside the hippocampus because their amnesia resulted from hypoxia secondary to heroin abuse. Yonelinas, et al. (19) wrote that “heroin overdose…produce(s) neurotoxic effects beyond those typically related to hypoxia.” Yet, the relevant citation (20) actually made the opposite statement: “permanent brain damage seems more likely to be caused by recurrent episodes of hypoxia during severe reactions to narcotics than to be related to direct neurotoxic effects of heroin.” While there is no reason to suppose that the two relevant patients in our study (G.W. and R.S.) have damage beyond the hippocampus, we reexamined the present data without G.W. and R.S. and found the same results as with the full group. Yonelinas, et al. (19) also drew attention to the severity of memory impairment in our patients, which suggested to these authors the possibility of damage beyond the hippocampus. Yet the severity of memory impairment in our patients is similar to the severity of impairment reported for other patient groups studied elsewhere who are described as having limited hippocampal damage (21, 22; here we compared our patients only to patients in these other studies with reported hippocampal lesions and not to patients that had larger lesions). Furthermore, volumetric measurements of the lateral temporal, frontal, and parietal lobe revealed no reductions in our patient group. The impression expressed by Yonelinas, et al. (19) that our patients are severely impaired may have originated from the unusually mild memory impairment in their own patients. Those patients (12) were selected based on a

history of hypoxia associated with cardiac arrest, not on the basis of MR data (which was not available) and not on the basis of their memory impairment. Indeed, many of the patients in this large group of 55 patients appeared to perform normally and to have no memory impairment (see individual data for the 55 patients in ref. 23).

Two other studies (24, 25) used the DPSD model to characterize the recollection and familiarity deficits associated with damage to structures other than the hippocampus. The first study, involving patients with mammillary body lesions (24), obtained familiarity estimates by the unusual step of converting d' estimates from the DPSD model to probabilities (d' is the distance between the means of two equal-variance Gaussian distributions and cannot be reasonably expressed as a probability). With this procedure, the model's familiarity parameter was calculated to be intact, and the recollection parameter was calculated to be differentially reduced. Yet, it is difficult to interpret the finding for the familiarity estimate, given the unusual method of calculating it. In the second study (25), a selective recollection deficit was reported for a single patient with damage to the anterior medial thalamus. Our own findings apply to patients with bilateral hippocampal lesions and showed that both parameters of the DPSD model (as well as both parameters of the UVSD model) were markedly reduced.

It is also worth mentioning that the UVSD model described our data far more accurately than did the DPSD model. This finding is consistent with many earlier studies of word list learning that have reached this same conclusion (26-29). In one instance involving memory for travel scenes taken from the internet,

the DPSD model performed better (28). It seems reasonable to use the better-fitting model to interpret the data. Accordingly, in terms of the better-fitting UVSD model, our findings suggest that hippocampal lesions reduce both the mean and the variance of the memory signal that is associated with the target items. This same result was obtained as memory weakened during the course of normal forgetting. Thus, the performance of patients with hippocampal lesions on memory tests reflects a broad impairment that is characteristic of weak memory.

## Materials and Methods

### *Experiment 1*

Participants. Five memory-impaired patients participated (Table 1), all with bilateral lesions thought to be limited to the hippocampus (CA fields, dentate gyrus, and subicular complex). K.E. became amnesic in 2004 after an episode of ischemia associated with kidney failure and toxic shock syndrome. 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. Patients G.W. and R.S. became amnesic in 2001 and 1998, respectively, following drug overdose and associated respiratory failure. J.R.W. became amnesic in 1990 following an anoxic episode associated with cardiac arrest.

Estimates of medial temporal lobe (MTL) damage were based on quantitative analysis of magnetic resonance (MR) images from 19 healthy males for the four male patients and 11 healthy females for patient L.J. (30). G.W., K.E., L.J., R.S., and J.R.W. have an average reduction in hippocampal volume of 48, 49, 46, 33, 44% respectively (all values >3 SDs from the control mean). On the

basis of two patients (L.M. and W.H.) with similar bilateral volume loss, for whom detailed postmortem neurohistological information was obtained, the degree of volume loss in the present patient group likely reflects nearly complete loss of hippocampal neurons (31). The volume of the parahippocampal gyrus is reduced by of 10, 11, -17, -5, 12% for G.W., K.E., L.J., R.S., and J.R.W., respectively (all values within 2 SDs of the control mean). These values differ slightly from the volumes reported previously for these patients and are based on newly published, more detailed guidelines for identifying the caudal border of the gyrus (32; for eight coronal MR images from each patient see Supplemental Materials).

Additional measurements, based on four controls for each patient, were performed for the frontal lobes, lateral temporal lobes, parietal lobes, occipital lobes, insular cortex, and fusiform gyrus (33). The only volume reduction in these regions >1.3 SDs of the control mean was the parietal lobe of patient R.S.

A control group of twelve healthy volunteers also participated (three females; mean age, 62.7 years; mean education, 14.3 years).

Materials and Procedure. Six hundred common English words (4-9 letters) served as stimuli (34). The words were used to construct six tests, each with 50 study words and 100 test words (50 targets from the study list plus 50 foils that were not previously studied). For testing, individual words served equally often as targets and foils, and the words were presented in a mixed order for each participant. The order of presentation of the six tests was also mixed across participants.

Controls were tested three times in a single session. To obtain robust

data, patients were tested six times in two sessions separated by an average of 5 months. The results were similar in the two sessions. After a 250-msec fixation cross, each word was presented on a computer screen for 2.5 sec and rated as pleasant or unpleasant on the keyboard. After 3-5 minutes of conversation to prevent rehearsal, the 50 target words were presented one at a time, intermixed with 50 foil words, and participants decided on a 6-point confidence scale whether each word had been presented before (1, sure new to 6, sure old). The end points of the confidence scale were labeled 1=”Definitely New” and 6=”Definitely Old” in the first session for the patients. The test was self-paced.

Data analysis. As discussed above, the DPSD model yields two parameters of interest: 1) the probability that a target will achieve a qualitatively distinct state of memory such that it is recognized with high confidence – a quantitative property of the memory signal that in this model is termed recollection (r); and 2) the distance between the average memory strength of targets and the average memory strength of foils, divided by the standard deviation of the two distributions (which is assumed to be identical). In the DPSD model this value is termed familiarity (d’). The UVSD model also yields two parameters of interest: 1) the ratio of the standard deviation of the target distribution to the standard deviation of the foil distribution ($\sigma_{target}/\sigma_{foil}$), and 2) the distance between the average memory strength of targets and the average memory strength of foils, divided by the standard deviation of the foil distribution. This value is termed d. Maximum likelihood parameter estimates for the DPSD and UVSD models were obtained for each participant by separately fitting both

models to each participant's confidence ratings using standard methods (35). For both models, 7 parameters were estimated (the two memory-relevant parameters discussed above plus 5 criteria specified by the confidence ratings).

*Experiment 2*

Participants. Nine healthy volunteers participated (2 females; mean age, 60.2 years; mean education, 14.5 years).

Materials and Procedure. Five hundred common English words (4-9 letters) served as stimuli (36). The 500 words (different from the words in Exp. 1) were used to construct five tests, each with 50 study words and 100 test words (50 study words plus 50 foils). For testing, individual words served equally often as targets and foils, and the words were presented in a mixed order for each participant. The order of presentation of the five tests was also mixed across participants.

Memory was tested using five separate recognition tests. Each participant was tested once each at study-test delays of 5 min, 1 hour, 1 day, 7 days, and 30 days. The order of the delays was mixed across participants. As in Experiment 1, maximum likelihood parameter estimates were obtained by fitting both models to the confidence data. Group data were analyzed because there were too few observations to fit the data from each participant individually.

*Experiment 3*

Participants. Five healthy volunteers (2 female; mean age, 60.6 years; mean education, 14 years) were tested on three separate occasions with a study-test delay of 1 day. In addition, 7 healthy volunteers (1 female; mean age,

56.2 years; mean education, 14.4 years) were tested on three separate occasions with a study-test delay of 7 days.

Materials and Procedure. Three hundred common English words (4-9 letters) served as stimuli (20). The 300 words (different from the words in Exp. 1 and 2) were used to construct three tests, each with 50 study words and 100 test words (50 study words plus 50 foils). For testing, individual words served equally often as targets and foils, and the words were presented in a mixed order for each participant. The order of presentation of the three tests was also mixed across participants. Data were analyzed as in Experiment 1, and parameter estimates for both models were calculated individually for each participant.

# ACKNOWLEDGEMENTS

Chapter 1, in full, is a reprint of the material as it appears in “Hippocampal damage impairs recognition memory broadly, affecting both parameters in two prominent models of memory” in PNAS: USA 110(16):6577-82. Dede, AJO, Wixted, JT, Hopkins RO, Squire, LR, 2013. The dissertation author was the primary investigator and author of this paper.

This work was supported by the Medical Research Service of the Department of Veteran Affairs and National Institute of Mental Health Grant MH24600. We thank Jennifer Frascino and Erin Light for assistance.

Table 1.1 Characteristics of Memory-Impaired Patients

| Patient | Age (years) | Education (years) | WAIS-III IQ | WMS-R Attention | Verbal | Visual | General | Delay |
|---|---|---|---|---|---|---|---|---|
| K.E. | 70 | 13.5 | 108 | 114 | 64 | 84 | 72 | 55 |
| L.J. | 74 | 12 | 101 | 105 | 83 | 60 | 69 | <50 |
| R.S. | 55 | 12 | 99 | 99 | 85 | 81 | 82 | <50 |
| G.W. | 52 | 12 | 108 | 105 | 67 | 86 | 70 | <50 |
| J.R.W. | 48 | 12 | 90 | 87 | 65 | 95 | 70 | <50 |

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

Table 1.2 Patient and control performance in Exp. 1

| | Patients | Controls |
|---|---|---|
| False Alarm Rate | .34 | .17 |
| Hit Rat | .61 | .84 |

Table 1.3 Control performance at variable delay intervals in Exp. 2

| Delay | 5m | 1hr | 1d | 7d | 30d |
|---|---|---|---|---|---|
| False Alarm Rate | .15 | .18 | .31 | .46 | .40 |
| Hit Rate | .84 | .77 | .66 | .60 | .47 |

Table 1.4 Patient and control performance in Exp. 1 and 3

| | Controls (1d) | Patients | Controls (7d) |
|---|---|---|---|
| Accuracy | .71 | .65 | .58 |
| False Alarm Rate | .22 | .34 | .37 |
| Hit Rat | .66 | .61 | .53 |

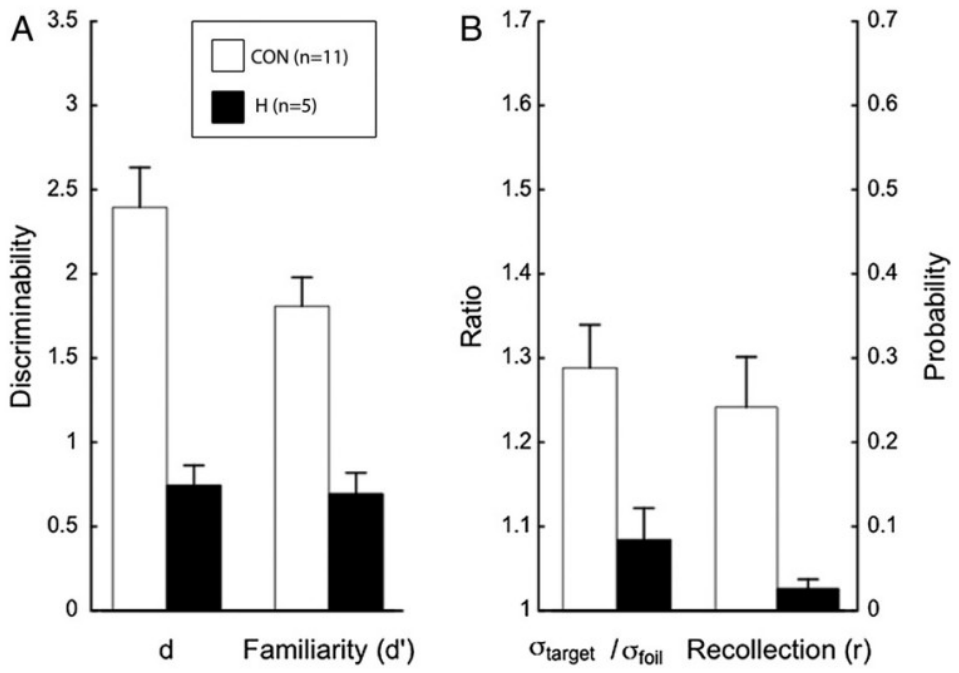


Figure 1.1 Parameter estimates for Exp. 1. Parameter estimates for recognition memory performance of controls (CON) and patients with hippocampal lesions (H) based on two prominent models. Both models yield two parameters of interest. The DPSD model yields estimates of familiarity and recollection. Familiarity is a discriminability estimate, d' (A), and recollection is a probability estimate, r (B). The UVSD model yields d, a discriminability estimate (A) and the ratio of the standard deviation of the target distribution to the standard deviation of the foil distribution, $\sigma_{target} / \sigma_{foil}$ (B). All estimates were lower for the patients than controls. Error bars show standard error of the mean.

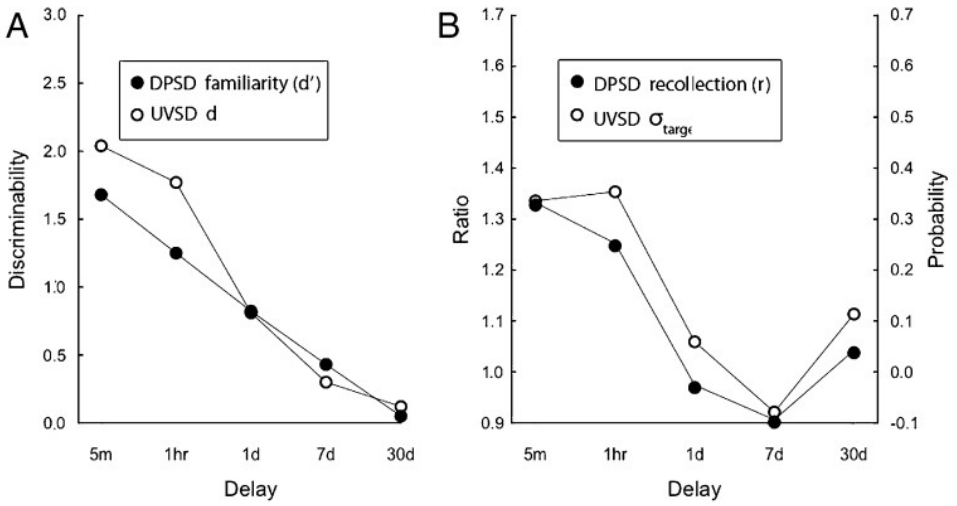


Figure 1.2 Parameter estimates for recognition performance of controls (CON, n=9) as a function of retention delay. The DPSD model yields estimates of familiarity, d' (A) and a probability estimate labeled recollection, r (B). The UVSD model yields d, a discriminability estimate (A) and the ratio of the standard deviation of the target distribution to the standard deviation of the foil distribution, $\sigma_{target} / \sigma_{foil}$ (B). In both models, the two parameters decrease as time passes after learning.

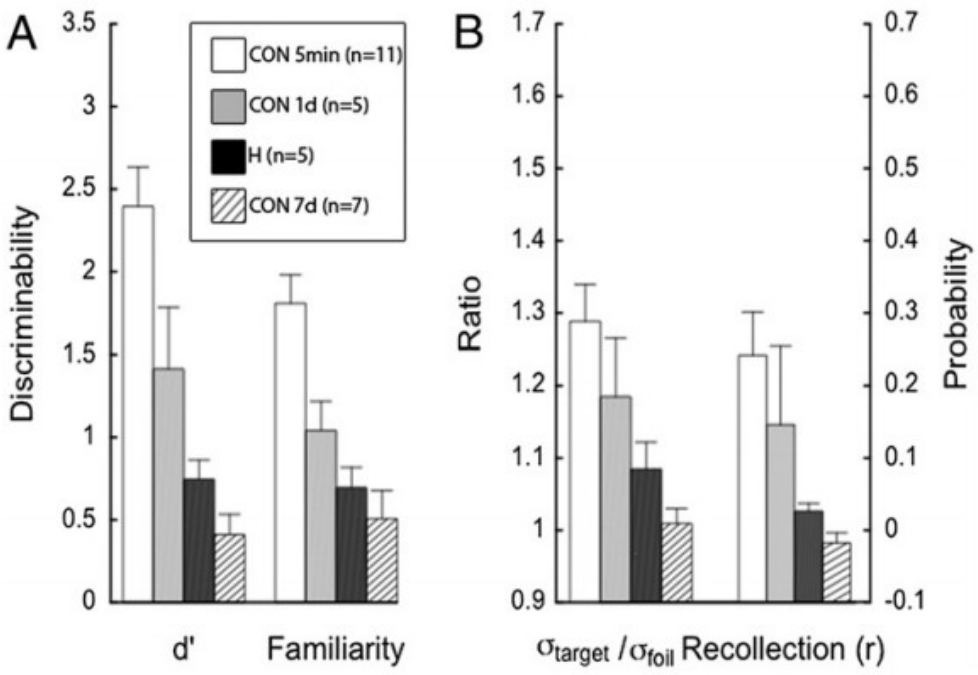


Figure 1.3 Parameter estimates for recognition performance of controls tested 1 or 7 days after learning (CON 1d, n=5; CON 7d, n=7) based on two models. Corresponding estimates from Figure 1 for controls (CON, n=11) and patients with hippocampal lesions (H, n=5) tested 3 minutes after learning are shown for comparison. At 1 day after learning, control performance was numerically better than performance of the patients tested 3 minutes after learning, while at 7 days after learning, control performance was numerically better than that of patients. The DPSD model yields estimates of familiarity, d' (A) and a probability estimate labeled recollection, r (B). The UVSD model yields d, a discriminability estimate (A) and the ratio of the standard deviation of the target distribution to the standard deviation of the foil distribution, $\sigma_{target} / \sigma_{foil}$ (B). All parameter estimates were higher for controls tested at one day after learning than for patients tested after 3 minutes. This pattern was reversed when controls were tested after 7 days. Error bars show standard error of the mean.

# CHAPTER 2

## Learning and remembering real-world events after medial temporal lobe damage

The hippocampus is important for autobiographical memory, but its role is unclear. Patients with hippocampal damage and controls were taken on a twenty-five minute walk on the University campus during which eleven planned events occurred. Memory was tested directly after the walk. In addition, a second group of controls took the same walk and were tested after one month. Patients with hippocampal damage remembered fewer details than controls tested directly after the walk but remembered a similar number of details as controls tested after one month. The details reported by patients had the characteristics of episodic recollection and included references to particular places and events. Patients exhibited no special difficulty remembering spatial details. Lastly, whereas both control groups tended to recall the events of the walk in chronological order, the order in which patients recalled the events was unrelated to the order in which they occurred. The findings illuminate the role of the hippocampus in autobiographical memory and in the spatial and nonspatial aspects of episodic recollection.

## Introduction

Autobiographical memory represents the experiences of our lives and provides our sense of self. We can mentally travel through time to re- experience

events from the past, and we can imagine events in the future. Without this faculty, our conscious life would be a series of unconnected moments.

The severely amnesic patient K.C. cannot remember a single personal event from his life and cannot describe what he did yesterday or what he might do tomorrow (36). K.C.'s amnesia was caused by a closed-head injury, which damaged the hippocampus and adjacent cortex, as well as regions of the frontal and parietal lobes (37). Though the extent of K.C.'s lesions makes it difficult to relate his impairment to anatomy, other work has studied autobiographical memory in patients with more circumscribed damage.

A number of studies have identified the hippocampus as an important structure for autobiographical memory (38-40), but its role remains unclear. Some findings emphasize its function in forming new memories about both events and facts (episodic and semantic memory) (41). Other studies suggest that the hippocampus is particularly important for the episodic content of autobiographical memory (e.g., time, place, and perceptual information) and that, as a result, patients with hippocampal damage must rely on semantic memory alone (42). Still other work suggests that the hippocampus is especially important for spatial cognition and that impaired autobiographical memory after hippocampal damage is due to a difficulty in constructing spatially coherent scenes (43).

Here, we describe a novel approach to the study of autobiographical memory and hippocampal function. Patients with hippocampal damage and healthy volunteers were taken individually on a twenty-five minute walk on the

University campus during which eleven planned events occurred (Figure 1). Directly after the walk, participants were asked for six-minute, narrative descriptions of what they could remember. Next, they constructed one-minute narratives in response to prompts about each of the eleven events. Lastly, they were given forty two-alternative, forced-choice questions about particular details of the walk. In this way, we assessed the accuracy and quality of memory for a real world event. Specifically, we evaluated the extent to which participants produced episodic memories, and we evaluated the quality of the memories in terms of their spatial and nonspatial content. To determine whether impairments exhibited by the patients reflect a qualitatively distinct deficit or a normal feature of weak memory, we also tested a second group of volunteers who took the same walk but were tested only after an interval of one month.

## Results

### *Six-minute narratives about the walk*

The patients with hippocampal lesions recalled fewer accurate episodic details about the walk than the CON-1 group ($t(10)=3.9$, $p<.01$) and about the same number of details overall as the CON-2 group tested after one month ($t(9)<1.0$, $p>.2$) (Table 1). Figure 2 shows that, except for details about time (which were rare), patients recalled fewer details than the CON-1 group in each category (event, space, and perception) ($ts(10)>2.3$, $ps<.05$), and they recalled about the same number of details in each category as the CON-2 group ($ps>0.1$). The single patient with large MTL lesions performed more poorly than the patients with hippocampal lesions (Table 1; $t(3)=6.6$, $p<.05$). Note that the

hippocampal patients and the MTL patient had no special difficulty reporting spatial details about the walk. Thus, the hippocampal patients scored 1.6, 1.5, and 1.3 standard deviations below the CON-1 mean for details in each category (event, space, and perception).

The patients (H and MTL) also recalled more inaccurate details than CON-1 and fewer unverifiable details (Table 1), but these differences did not reach significance ($p<0.08$ for inaccurate details; $p>0.2$ for unverifiable details). It was also the case that patients repeated themselves more during narrative construction than did CON-1 ($t(10)=2.4$, $p<.05$) (Figure 2B).

To assess memory for the temporal order in which the events had occurred, we plotted the order in which the 11 events of the walk were described. Figure 3A provides this information for the H and MTL patients (combined) and for CON-1. The CON-1 group described events approximately in the order in which they had occurred ($r=.95$, $p<.05$). By contrast, the order in which patients described events was unrelated to the order in which they had occurred ($r=-.47$, $p>.2$). Figure 3B shows corresponding data for CON-2 in comparison to the data for CON-1. Group CON-2, like CON-1, described events in the order they had occurred ($r=.91$, $p<.05$).

*One-minute narratives about each of the 11 events*

Figure 4 shows the number of accurate details that were recalled during one minute in response to prompts about each event of the walk. Patients with hippocampal lesions retrieved significantly fewer details than CON-1 about every event (ps<.05), except event 11 (the drink). The events that were most

memorable for CON-1 were also the most memorable events for the patients (Figure 5)($r=.81$, $p<.05$).

Unlike in the six-minute narratives, the hippocampal patients retrieved marginally fewer accurate details overall than CON-2 (3.9 vs. 5.4 details per event, $p=.06$). This finding appeared to depend on differences in how well the two groups remembered the more salient events that appear to the right in Figure 4. To confirm this observation, events were divided into two groups: the five events best remembered by CON-1 and the five events least remembered. While the scores of the hippocampal patients matched the scores of the CON-2 group for the least remembered events, the CON-2 group remembered the salient events better than the patients (interaction of group X salience: $F(1,9)=9.4$, $p<.05$).
As with the six-minute narratives, we evaluated performance in each content category averaged across all events (event, space, and perception)(Time details were rare and were not counted; <0.1 detail/event in each group). The H group recalled fewer event and perception details than CON-1 ($ts(10)>3.0$, $ps<.05$, for space details: $p>.1$). The CON-1 group produced an average of 2.9, 1.4, and 4.4 accurate details per event in the event, space, and perception categories, respectively. For the H group, the corresponding values were 1.4, 0.6, and 1.9 details, and for CON-2 the values were 1.6, 1.4, and 2.4 details. The H group scored 2.7, 1.2, and 1.3 standard deviations below the CON-1 mean in the event, space, and perception categories, respectively.

Patients produced more inaccurate details than CON-1 (1.6 vs. 0.5 details per event; $t(10)=3.4$, $p<.05$) and about the same number of inaccurate details as

CON-2 (1.6 vs. 1.1 details per event; p>.1). Participants reported few unverifiable details during the one-minute narratives (range of means across groups = 0.6-1.5 details per event; no between-group differences, ps>.1).

In view of the suggestion that the hippocampus is uniquely important for binding items to contexts (44), we asked whether the patients had difficulty connecting remembered details to the appropriate events. That is, did patients mix details between events more frequently than controls? Accordingly, for the one-minute narratives we counted how often participants reported details about events other than the event being asked about. The hippocampal patients did this only rarely, numerically less often than the controls (0.2 times/event vs. 0.3 times/event). Thus, we found no evidence that the hippocampus is especially important for binding items to contexts.

Performance of the patient with large MTL lesions was variable. While he produced fewer details per event overall than CON-1 (4.4 vs. 8.8), he nevertheless did well describing three of the events (cup, shoe, and statue). However, he often appeared to remember only a fragment about an event and then generated a narrative consisting of plausible guesses and far-fetched comments (in reference to the statue: “It wasn’t a covered wagon”). In addition, his narratives included more than twice as many inaccurate details as the narratives of any other group (3.3/event), he repeated himself frequently (Figure 2B), and he frequently incorporated remarks about events other than the event he was asked about (four times more often than any other group). Two-alternative, forced-choice questions about the walk

Figure 6 shows the results for the two-alternative, forced-choice test. Overall, patients with hippocampal lesions performed more poorly than CON-1 ($t(10)=2.4$, $p<.05$) and performed similarly to CON-2 ($p>.2$). With the exception of questions about time, the hippocampal patients performed poorly in all content categories. Their scores were 2.1, 1.4, and 2.5 standard deviations below the CON-1 mean for questions about events, space, and perception, respectively. The patient with large MTL lesions performed poorly overall, but did well on questions about space.

## Discussion

Patients with hippocampal damage remembered fewer details than controls about 11 events that occurred during a guided walk on the University campus. This impairment was evident in six-minute narratives that participants constructed about the walk, directly after returning to the laboratory (Figure 2). Patients also recalled fewer details than controls in prompted one-minute narratives about each of the 11 events (Figure 4), and they performed poorly on 40 two-alternative, forced-choice questions about specific details from the walk (Figure 6). In many respects, performance of the patients resembled the performance of a group (CON-2) that was tested one month after the walk. Thus, in their six-minute narratives patients recalled about the same number of total details as the CON-2 group (Table 1), and they recalled a similar number of details in each content category (event, space, perception, and time)(Figure 2). However, in one respect patient performance differed sharply from the performance of either the CON-1 or CON-2 groups. Whereas both control groups

tended to recall the events of the walk in the order that they occurred, the order in which patients recalled the events was unrelated to the order in which the events occurred (Figure 3).

Despite their memory impairment, the patients did remember a significant number of event, space, and perception details in both the six- minute (Figure 2) and one-minute narratives. These details had the characteristics of episodic recollections and included references to particular places and events. For example, G.W. remembered that the bicycle “had a light on the front.” L.J. remembered that the books in the library had been “further down on the shelf, and it seems like they were white.” In addition, the events that were most memorable for the controls were also most memorable for the patients (Figure 5), suggesting that patients and controls experienced the salience of the events similarly.

The behavior of our patients was distinct from that observed with the densely amnesic patient K.C. and others like him, who cannot remember any personal events (36, patient D.R.B. in 45, patient R.F.R. in 46, patient G.T. in 47). If damage to the hippocampus were the cause of such a severe condition, then our patients’ narratives should have been devoid of episodic content, lacking specificity about the events of the walk. Their narratives should have amounted to a collection of factual statements related to what was seen on the walk. However, the narratives produced by our patients contained vivid episodic content. Accordingly, our results are at odds with the idea that the hippocampus is specifically necessary for the episodic content of recollection (42). The

difference between our patients and more severely impaired patients (e.g., K.C.) likely depends on differences in the locus and extent of their brain damage. Indeed, patient K.C. and all the patients cited above have damage that extends beyond the MTL to involve other regions, especially in frontal and lateral temporal cortex (also see 36, 48).

The question arises whether the capacity for episodic recall reflects partially preserved hippocampal function in patients with a reduction in hippocampal volume averaging only 45%. This possibility seems unlikely for two reasons. First, patient G.P., who has virtually no detectable hippocampus, was capable of some episodic recollection. Second, for two different patients, neurohistology revealed complete loss of hippocampal neurons despite only partial reduction in hippocampal volume (49). Thus, partial hippocampal volume loss in memory-impaired patients can reflect complete hippocampal dysfunction. The impairment exhibited by the patients was evident to a similar degree in three of the four content categories, event, space, and perception (Figure 2). Notably, patients exhibited no special difficulty in the production of spatial content, not in the six-minute narratives and not in the one-minute narratives. Indeed, every patient provided some accurate and specific spatial details. For example, K.E., when describing the student with the bike lock (Event 6), accurately remembered: “he was walking west, and we were going east.” G.W. accurately reported that there were “muffins on the counter next to the bananas” (Event 9). Even G.P., with large MTL lesions, accurately reported that the statue had been “8 to 10 feet high…water was coming out of the top.” In comparison to CON-1,

the patients had no more difficulty with the questions that asked about space than with questions about other features of the events (Figure 6). Taken together, our results provide little support for the idea that the hippocampus has a special role in constructing spatial scenes or in recollecting spatial details from memory (43).

Although the patients were able to organize the details from the walk into distinct coherent events, they differed markedly from controls in that they did not (in the 6-minute narratives) describe events in the same sequence in which they had occurred (Figure 3A). Even controls tested after one month still recalled events in approximately chronological order (Figure 3B). Thus, difficulty with temporal order information was not a simple consequence of weak memory. We suggest that the inability of the patients to remember the temporal sequence of the walk may have reflected their inability to bridge temporal gaps between discrete events. Specifically, the gaps between events would have challenged working memory capacity (50). As events unfolded over time, working memory was continuously overwritten, which would have made it difficult to link the separate events, except by relying on long-term memory. The patients with hippocampal damage would have been disadvantaged because they could not have used long-term memory to learn about the order of events as they proceeded along the walk.

Note that this finding is not evidence for a selective impairment in memory for temporal information. Rather, the results suggest that patients would have been especially impaired on any test that assessed “global” information about the

relationship between events (temporal, spatial, or perceptual relationships). In contrast, for tests that assess "local" information about individual events (and most of our tests did), the information could initially have been acquired within working memory. The information would then be available for transfer to long-term memory to the extent that long-term memory can be established after hippocampal damage. Importantly, as indicated in Figures 2, 4, and 6, patients with hippocampal damage typically retain some ability to learn lists, locations, and other material.

In summary, patients with damage to the MTL learned and remembered fewer details about real-world events than controls when testing occurred directly after the events occurred. In many respects, the patients performed similarly to controls tested after a delay of one month (Figures 2 and 4). Despite their impairment, patients recalled many accurate and specific episodic details about events of the walk. They also remembered details from all content categories (Figure 2), and there was no evidence of a special difficulty reporting spatial content about the events. By contrast, patients were strikingly deficient at remembering the temporal sequence in which events occurred during the walk (Figure 3A). The latter result suggests that the hippocampus is particularly important for bridging gaps between events and discovering relationships between separate events (temporal, spatial, or perceptual).

## Materials and Methods

### *Participants*

Five memory-impaired patients participated (Table 2), four with bilateral

medial temporal lobe lesions limited to the hippocampus (CA fields, dentate gyrus, and subicular complex) and one with larger medial temporal lobe lesions. Patients G.W. and D.A. became amnesic in 2001 and 2011, respectively, following drug overdose and associated respiratory failure. Patient KE 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. Patients K.E., L.J., G.W., and D.A. have an average bilateral reduction in hippocampal volume of 49%, 46%, 48%, and 35%, respectively. On the basis of findings from two patients (L.M. and W.H.) with similar bilateral volume loss in the hippocampus for whom detailed postmortem neurohistological information was obtained (49), the degree of volume loss in these four patients may reflect nearly complete loss of hippocampal neurons. The volume of the parahippocampal gyrus (including temporopolar, perirhinal, entorhinal, and parahippocampal cortices) is reduced by 11%, -17%, 10%,  and -5% for K.E., L.J., G.W., and D.A., respectively. These values are based on published guidelines for identifying the caudal border of the parahippocampal gyrus (51). The negative values indicate instances where the volume was larger for a patient than for controls. 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 (52). 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 description of the lesions, are presented elsewhere (53).

Two groups of healthy volunteers also participated. One group (CON-1) was tested directly after the walk (n=8; 1 female; mean age = 60.8 years; mean education = 13.8 years). The other group (CON-2) was tested one month after the walk (n=7; 3 females; mean age = 64.1; mean education = 14.8 years). All procedures were approved by the Institutional Review Board at the University of California at San Diego, and participants gave written informed consent prior to participation.

*Procedure*

Each participant was taken for a 25-minute walk on the campus of the University of California, San Diego. Before the walk, participants were told that their memory would be tested afterwards for everything that occurred during the walk. However, they would not need to remember any part of conversations. A fixed order of 11 events occurred during the walks (Figure 1). The experimenter was the “actor” for each event (she discarded the cup, found the book, etc.). The sixth event of the walk required a confederate, who provided a bike lock and asked that the experimenter lock his bike. The walks were scheduled at either 10:30am or 1:30pm (not during class changes or lunch time) to standardize the background environment as much as possible.

Upon returning to the laboratory, patients and controls in the no-delay condition were tested for their memory of the walk. The procedure was identical for controls tested one month later. Participants were first given up to six minutes

to describe in as much detail as possible all that they could remember about the walk. The experimenter provided support during narrative construction by probing for detail (54, 55).

Next, the experimenter provided a prompt for each of the 11 events of the walk (e.g., “What happened at the vending machine?”). In response to each prompt, participants were given up to one minute to describe the event in as much detail as possible. The instructions emphasized that participants could repeat details they had already reported in the six-minute narrative. Last, participants were asked 40 two-alternative, forced-choice questions about the 11 events of the walk. The questions followed the order in which the events had occurred. Before asking questions about a particular event, the event in question was first identified (e.g., The next few questions will be about the statue). Seven questions asked about the event itself (e.g., Did we find a quarter or a dime?). Thirteen questions asked for perceptual information (e.g., Were the doors to the building wooden or glass?). Thirteen questions asked for spatial information (e.g., What kind of vending machine was on the right: snack or drink?). Seven questions asked for temporal information (e.g., Did it take less than 30s or more than 3m to walk from the bike to the fountain?). All responses were recorded.

*Narrative Scoring*

Narratives were first partitioned into details as described previously (40, 55-57). Each detail was then scored as reflecting episodic memory, semantic memory, repetition, or remembered thoughts. Episodic details described aspects

of specific events. Semantic details described facts that contextualized events. Participants produced few semantic details, perhaps because little context is needed when one describes recent events to someone who also experienced them. Semantic details (<6.4/group/narrative) were not considered further. Repetitions were details that repeated information from earlier in the narrative. Thoughts described introspective commentary (e.g., “I liked that place”) and were not analyzed further. Next, following methods described in other studies (56, 57), each episodic detail was categorized according to its content: event, space, time, or perception. Event details described persons or actions. Spatial details described places or spatial relationships between objects or persons. Time details described temporal information about an event (e.g., “It was real quick”). Perceptual details described objects, colors, weather, or other sensory information.

We then assessed the accuracy of each detail. Details were scored as “accurate” if they could be verified as having happened on the walk (e.g., “You found a quarter in the machine”). Details were scored as “inaccurate” if they did not happen on the walk (e.g., “We stopped at a Pepsi machine” [it was a snack machine]). Details were scored as “unverifiable” if it was not possible to determine their accuracy. The unverifiable details were usually unrelated to any of the 11 scheduled events and involved objects, actions, or pieces of conversation (e.g., “A girl walking on the path had red shoes”). A.D. partitioned the six-minute narratives into details and assigned them to content categories. A second person blind to group membership scored a randomly selected 32% of

the data (2 participants from each group, 6 participants). Across participants and content ratings, the correlation between scores was .92 and Cronbach's α was .96. A.D. scored the one-minute narratives.

ACKNOWLEDGMENTS

Chapter 2, in full, has been submitted for publication of the material as it may appear in PNAS: USA by Dede, AJO, Frascino, JC, Wixted, JT, Squire, LR. The dissertation author was the primary investigator and author of this paper. This work was supported by the Medical Research Service of the Department of Veterans Affairs, and NIMH Grant 24600. We thank Ryan Ward and Christine Smith for assistance.

Table 2.1 Total details

| Group | Accurate | Inaccurate | Unverifable |
|---|---|---|---|
| CON-1 | 56 (5.3) | 4 (1.1) | 10 (4.5) |
| CON-2 | 32 (5.8) | 4 (1.4) | 7 (3.6) |
| H | 26 (2.7) | 10 (6.2) | 5 (2.3) |
| MTL | 18 | 8 | 5 |

Mean number of accurate, inaccurate, and unverifable details produced by each group during a six-minute narrative description of the walk. Standard errors are in parentheses. CON-1 = controls tested directly after the walk. CON-2 = controls tested one month after the walk. H = patients with hippocampal lesions. MTL = a patient with large medial temporal lobe lesions.

Table 2.2 Characteristics of Memory-Impaired Patients

| Patient | Age (years) | Education (years) | WAIS-III IQ | WMS-R | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Attention | Verbal | Visual | General | Delay |
| D.A. | 31 | 12 | 90 | 87 | 65 | 95 | 70 | 56 |
| K.E. | 73 | 13.5 | 108 | 114 | 64 | 84 | 72 | 55 |
| L.J. | 77 | 12 | 101 | 105 | 83 | 60 | 69 | <50 |
| G.W. | 55 | 12 | 108 | 105 | 67 | 86 | 70 | <50 |
| G.P. | 68 | 16 | 90 | 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.

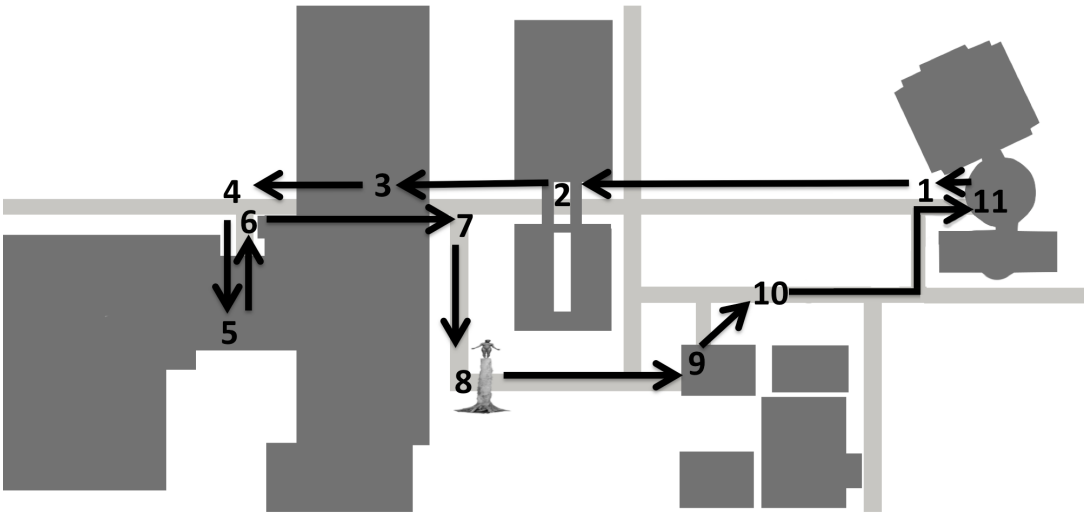


Figure 2.1 Map of 11 events that occurred during a guided walk. 1: discard a cup. 2: find change in a vending machine. 3: view portraits of Department chairs. 4: point out coffee cart. 5: find book on the second floor of the library. 6: receive bike lock from student. 7: lock up bike. 8: view statue. 9: buy banana in cafe. 10: stops to tie shoes. 11: drink from water fountain. Sidewalks are light grey. Buildings are dark grey. Arrows indicate the path taken during the walk.

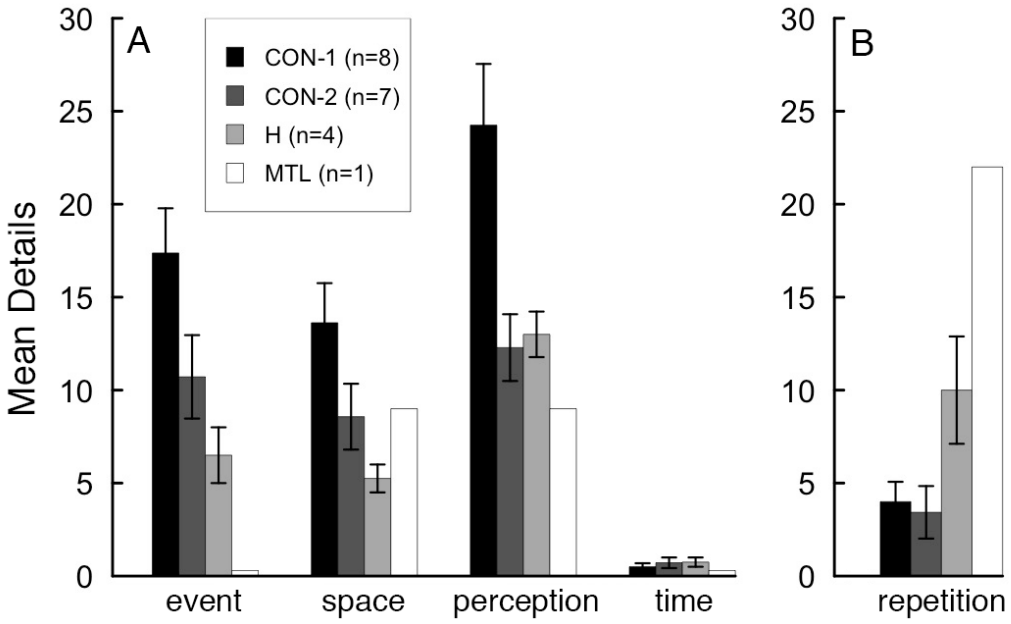


Figure 2.2 Number of accurate details produced in six-minutes. A. Details were assigned to one of four categories according to their content. B. The number of details that were repeated during the narrative. CON-1 = controls tested directly after the walk. CON-2 = controls tested one month after the walk. H = patients with hippocampal lesions. MTL = a patient with large medial temporal lobe lesions. Error bars show standard error of the mean.

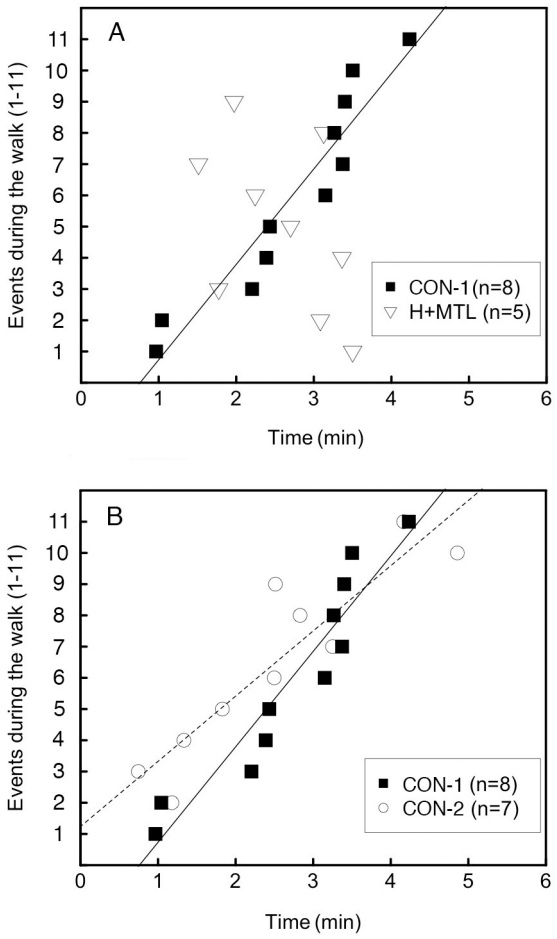


Figure 2 . 3 Temporal organization of narratives. The data points show when, on average, the events from the walk were described during the six-minute narratives. The two control groups tended to describe events in the order that they occurred. The order in which the patients described events was unrelated to the order in which the events occurred. Lines represent significant fits to the data. A) CON-1 = controls tested directly after the walk. H = patients with hippocampal lesions. MTL = a patient with large medial temporal lobe lesions. The patients described only 9 of the 11 events and omitted events 10 and 11. B) CON-1 together with controls tested one month after the walk (CON-2). The CON-2 group described only 10 of the 11 events and omitted event 1.

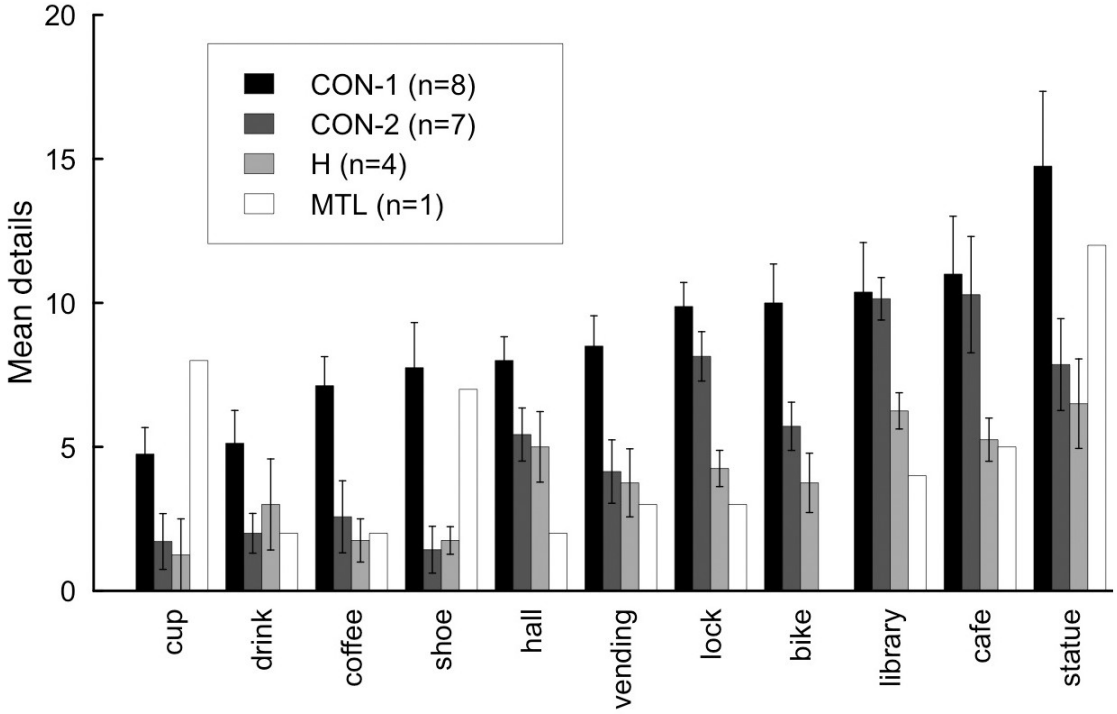


Figure 2 . 4 Number of accurate details per event. Number of accurate details produced in one-minute narratives when participants were asked about each event separately in response to a prompt. The data are arranged according to how well the CON-1 group remembered each event. CON-1 = controls tested directly after the walk. CON-2 = controls tested one month after the walk. H = patients with hippocampal lesions. MTL = a patient with large medial temporal lobe lesions. Error bars show standard error of the mean.

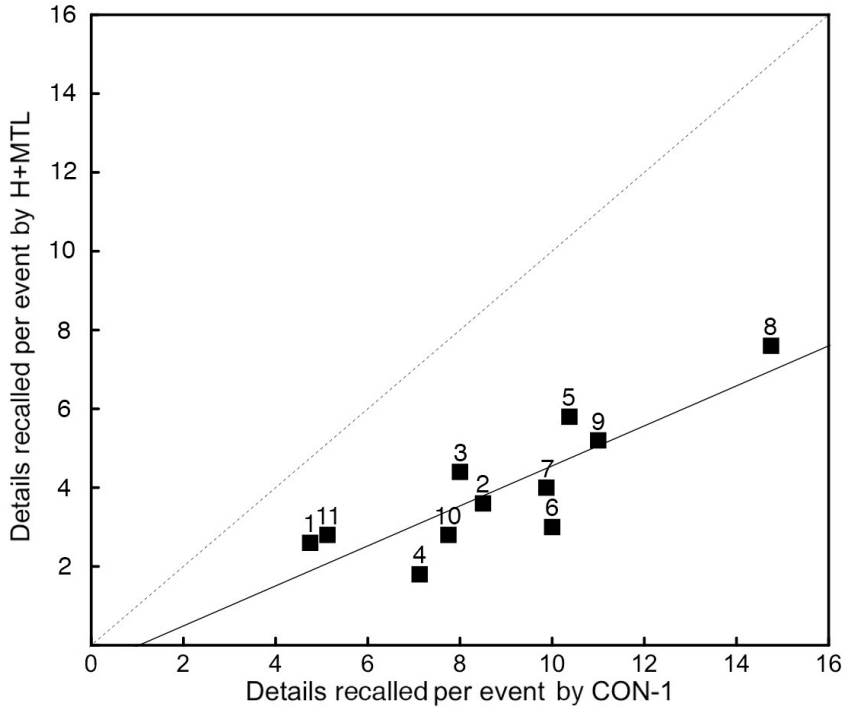


Figure 2 . 5 Accurate details per event for CON-1 vs. patients. Details recalled during one-minute narratives about each event in response to a prompt (also see Figure 4). The events best remembered by CON-1 were also the events best remembered by the H and MTL patients. The numbers identify each event (Figure 1). The scatter plot shows the number of accurate details per event produced by the patients as a function of the number of details produced by CON-1. For example, CON-1 recalled 7.1 details about event 4 (coffee cart) and 10.4 details about event 5 (library). The patients recalled 1.8 and 6.2 details about these same two events. CON-1 = controls tested directly after the walk. H = patients with hippocampal lesions. MTL = a patient with large medial temporal lobe lesions.

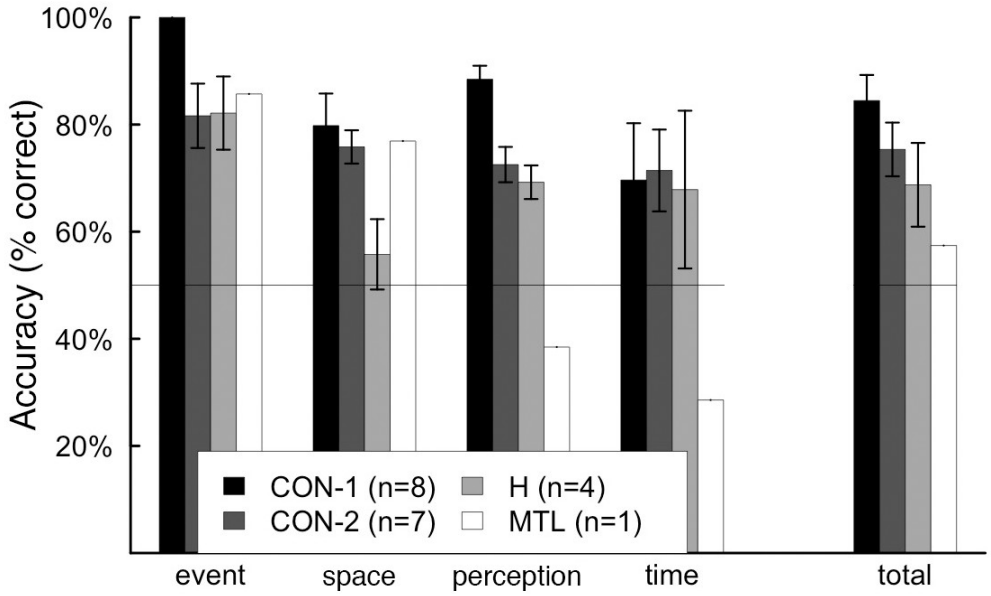


Figure 2 . 6 Performance on two-alternative forced-choice questions. There were four types of questions, querying different types of information. CON-1 = controls tested directly after the walk. CON-2 = controls tested one month after the walk. H = patients with hippocampal lesions. MTL = a patient with large medial temporal lobe lesions. Error bars show standard error of the mean. Horizontal line represents chance performance.

# CHAPTER 3

## Autobiographical memory, future imagining, and the medial temporal lobe

In two experiments, patients with damage to the medial temporal lobe (MTL) and healthy controls produced detailed autobiographical narratives as they remembered past events (recent and remote) and imagined future events (near and distant). All recent events occurred after the onset of memory impairment. The first experiment aimed to replicate the methods of Race et al. (57). Transcripts from that study were kindly made available for independent analysis, which largely reproduced the findings from that study. Our patients and patients from the earlier study produced fewer episodic details than controls, but patients from the earlier study were more impaired than our patients. Patients in both groups had difficulty returning to their narratives after going on tangents, suggesting that anterograde memory impairment may have interfered with narrative construction. In Experiment 2 the experimenter used supportive questioning to help keep participants on task and reduce the burden on anterograde memory. This procedure increased the number of details produced by all participants and rescued the performance of our patients for the distant past. Neither of the two patient groups had any special difficulty producing spatial details. The findings suggest that constructing narratives about the remote past and the future does not depend on MTL structures, except to the extent that anterograde amnesia affects performance. The results further suggest that different findings about the status of autobiographical memory likely depend on

differences in the location and extent of brain damage in different patient groups.

## Introduction

Episodic memory affords the capacity to recollect past events that occurred at a particular time and place (58). In humans, episodic recollection allows for the re-experiencing of an event through a process of “mental time travel” (59). The hippocampus is known to be important for episodic memory, but its specific contribution is unclear. In one view, the hippocampus is needed for the formation and consolidation of long-term memory for a limited time after learning (60). This view finds support in reports that patients with hippocampal damage were intact at recollecting episodes from early life (and impaired only for more recent time periods (61-63). Another view holds that episodic memories remain dependent on the hippocampus so long as they persist (64, 65). In support of this idea, patients with hippocampal damage were sometimes impaired at recollecting events from early life (66, 67). A third view follows from the suggestion that the same process that enables recollection of the past is also engaged when imagining the future (68-71). In two studies, patients with hippocampal damage were impaired at imagining new experiences or future events (66, 70; but see 61). This deficit has been proposed to be part of a broader impairment in the ability to construct spatially coherent scenes (71).

The present study explored these divergent views of hippocampal function by asking healthy controls and patients with hippocampal damage to remember past episodes (near past and distant past) and to imagine future episodes (near

future and distant future). In the first experiment, we aimed to replicate the methods of Race et al. (57), where memory-impaired patients were impaired at recollecting the past and also imagining the future. The original transcripts from the earlier study were also made available to us, and we scored them with the same methods used to score our own data. In this way, it was possible to evaluate the importance of how narratives are elicited and scored. Our scoring largely reproduced the earlier findings. Both our patients and the patients from the earlier study (57) were impaired at producing episodic details during narrative construction. The deficit was more severe in the patients from the earlier study. Both patient groups also tended to lose track of their narratives and to go on tangents. To explore the significance of this finding, in the second experiment the experimenter helped keep participants on task during narrative construction through the frequent use of supportive questioning. With this method, the performance of our patients was intact for all time periods except the near past.

## Results

### *Experiment 1*

Figure 1 shows the number of episodic and semantic details in Experiment 1 as participants recalled the past and imagined the future. Repetitions, metacomments, and irrelevant details were not counted (see Methods). Corresponding results from our independent analysis of data from Race et al. (57) are also illustrated. Data for episodic and semantic details in our study were analyzed using three-way, mixed-factorial ANOVAs (patient vs. control, past vs. future, distant vs. near). For episodic details, the overall difference between

patients and controls did not reach significance ($F(1,13)=3.3$, $p=.09$). However, relative to controls, patients had more difficulty with past time periods than with future time periods (interaction of group x temporal direction: $F(1,13)=12.5$, $p<.01$). Post hoc t-tests revealed differences between patients and controls in both past time periods, but not in future time periods. In addition, both groups produced more details for past time periods than for future time periods ($F(1,13) = 41.5$, $p<.001$). None of the other main effects or interactions approached significance ($ps>.1$). For semantic details, patients were marginally impaired overall ($F(1,13)=4.2$, $p=.06$). There were no other main effects or interactions ($ps>.1$). The single patient with large MTL lesions performed similarly to the patients with hippocampal lesions.

An important question is whether patients with hippocampal damage had particular difficulty producing spatial details in their narratives in comparison to other kinds of details. Figure 2 shows the number of details per narrative in all five categories of episodic content (see Methods). The data were analyzed using a 2 X 5 mixed-factorial ANOVA (two groups, five content categories). Some categories contained more details than others ($F(4,52)=64.5$, $p<.01$), but this effect was similar for the patients and controls (no interaction of group x category, $p>.1$), and there was no indication that patients had special difficulty producing spatial details. Indeed, the largest difference between patients and controls was in time details (Cohen's $d = 1.1$), and the difference in spatial details was among the smallest (Cohen's $d = .6$). The findings were similar in the study by Race et al. (57). Although their patients were impaired at producing details in

each of the five categories, the impairment in spatial details was the smallest (Cohen's d = .6).

Anterograde amnesia may have contributed to task difficulty by impairing the ability to keep the organization of a narrative in mind during narrative construction. We tested for this possibility with a novel analysis by asking how often participants were able to return to the central event of their narratives after going on tangents (Figure 3). Our patients were deficient at recovering from tangents ($t(13)=3.6$; $p<.01$), and the same effect is evident in the data from Race et al. (57). Although our patients had difficulty recovering from tangents, the frequency with which they went on tangents was similar for patients and controls (mean = 0.6 vs. 0.9 tangents per narrative; $p>.2$).

*Experiment 2*

If anterograde amnesia contributed to the impaired performance of the patients in Experiment 1, then patient performance should be better in Experiment 2. For Experiment 2, the experimenter provided extensive support during narrative construction in the form of questioning and probing for details. This procedure helped keep participants on task as they developed their narratives.

*Episodic and semantic detail counts*

Figure 4 shows the number of episodic and semantic details in Experiment 2 as participants recalled the past and imagined the future. Participants produced many more details in Experiment 2 than in Experiment 1. The main finding was that patients were strikingly deficient at remembering episodic details from the

near past, but they did well at remembering the distant past and imagining the future. An ANOVA (patient vs. control, past vs. future, distant vs. near) confirmed this specific deficit in the near past (interaction of group x temporal direction x temporal distance: $F(1,13)=7.6$, $p<.05$). Post hoc t-tests also revealed a difference between patients and controls in the near past ($t(13)=3.2$, $p<.01$) but not in other time periods ($ps>.1$). Lastly, there was an interaction of group x temporal direction ($F(1,13)=33.4$, $p<.001$), indicating that the patients did a little better imagining the future than remembering the past, whereas controls exhibited the opposite pattern. The patient with large MTL lesions performed like the patients with hippocampal lesions. With respect to semantic details, patients and controls performed similarly, and an ANOVA yielded no significant findings.

Figure 5 shows the number of details per narrative in each of the 5 episodic content categories (as in Experiment 1). The patients included spatial details in their narratives as frequently as controls. A 2 X 5 ANOVA (patient vs. control, 5 episodic content categories) yielded a main effect of content category ($F(4,52)=57.9$, $p <.001$), reflecting the tendency of both groups to produce more event and perceptual details than other kinds of details. There was no group effect and no interaction. Post-hoc t-tests revealed no differences between patients and controls for any content category ($ps>.2$).

Although the support provided in Experiment 2 successfully encouraged participants to produce long and detailed narratives, the question naturally arises whether these details, to any extent, reflected an influence of the experimenter on how patients and controls constructed their narratives. This possibility seems

unlikely because the number of probes provided to participants was virtually identical for all time periods within each group. However, patients did receive more probes per narrative than controls did (29.6 vs. 18.3; $p<.001$). To test whether patients succeeded in part by incorporating information suggested by the experimenter into their narratives, we categorized all probes from the experimenter as general or specific (see Methods). If patients often incorporated information suggested by the experimenter, then they should have produced more details in response to specific probes than in response to general probes. However, this did not occur. An ANOVA (patient vs. control, general vs. specific) yielded only a main effect of group ($F(1,13)=19.3$, $p<.001$) but no interaction. That is, patients produced fewer details in response to each probe than did controls (2.1 vs. 3.5), but the number of details produced was about the same when the probe was general and nonspecific as when the probe was specific (even when the probe included an explicit suggestion about content). For controls, the average number of details in response to each probe was 3.7 and 3.4 for general and specific probes, respectively. For patients, these numbers were 2.2 and 2.2 for general and specific probes. Thus, although patients received more probes than controls, there was no evidence that these probes advantaged the patients by suggesting content that they could incorporate into their narratives. We suggest that the probes, whether general or specific, served mainly to keep participants engaged in the task.

## Discussion

Participants were invited to construct detailed personal narratives as they remembered past events and imagined future events. We tested seven memory-impaired patients and nine controls, and also rescored transcripts kindly made available to us from an earlier, similar study (57). Our patients produced fewer episodic details from the past than controls but were intact at imagining the future. Patients from the earlier study exhibited a more severe deficit that affected all time periods (Fig. 1). In addition, both patient groups had difficulty returning to the central event of a narrative after going on a tangent (Fig. 3), suggesting that anterograde amnesia may have affected narrative construction. To explore this possibility, in Experiment 2 the experimenter provided participants with supportive questions to keep them on task and to reduce the burden on anterograde memory. This manipulation markedly increased the number of details produced by all participants and rescued the performance of our patients as they recollected memories from the distant past (Fig. 4). Patients were impaired only for the near past. In summary, in Experiment 2 when patients with MTL damage recollected memories from the distant past and when they imagined the future, they produced narratives that contained as much detail as control narratives.

For the near past, all the events that patients were asked about had occurred after the onset of their memory impairment. Accordingly, memory for events from the near past would not be expected to be available, with or without experimenter support. By contrast, for the distant past, memory was queried for

events that occurred long before the onset of memory impairment. We suggest that without experimenter support in Experiment 1, impaired anterograde memory challenged the ability to produce detailed and coherent narratives. In Experiment 2, experimenter support diminished the effect of anterograde memory impairment and improved performance.

The possibility that anterograde amnesia might directly impair narrative constructions about the past or the future has been considered previously (72-75). Several observations support this idea. First, in an earlier study, patients repeated themselves more often than controls when they recalled the past (76). In another study, patient KC was able to distinguish true from false details about familiar fairy tales that he would have learned as a youth, but his narratives lacked detail when he tried to recount the stories himself (73). In still another study, memory-impaired patients were asked to imagine new experiences as well as to construct narratives about a picture that was presented to them (74). Descriptions of the scene were impoverished, and this impairment appeared to explain the difficulty that patients also had in imagining new experiences. Lastly, Experiment 1 showed that both our patients and the patients from the earlier study (56) had difficulty returning to their narratives after going on a tangent (Fig. 3).

Additional evidence for the impact of anterograde amnesia on narrative construction is that our patients frequently made statements discontinuous with what had been said earlier in the narrative (patients: 1.6 instances/narrative; controls: 0.2 instances/narrative; $p<.05$). For example when asked to imagine a

future event, one patient described learning to play bridge with friends. However, in the midst of the narrative, the card game changed from bridge to pinochle. Another patient, while imagining the future graduation ceremony of a grandson from college, abruptly began to describe watching him in a soccer game. These and other examples suggest that, due to their anterograde amnesia, patients forgot aspects of their narrative and introduced discontinuous content.

The question arises why impaired anterograde memory might sometimes affect the ability to recollect the past but not the ability to imagine the future (our data, Experiment 1). One possibility is that anterograde memory impairment has a greater influence on narrative construction when narratives are relatively long. In our Experiment 1, participant narratives about the distant past contained 46% more details than the narratives about the future. Another possibility follows from the fact that narratives about future events need not depend on any particular memory. As has been suggested (77), future imagining typically involves constructing a novel recombination of information from multiple different memories. By contrast, narratives about the past are based upon memory of an already experienced event. If one loses track of a narrative while recalling the past, one must remember what event to return to. However, if one loses track of a narrative while imagining the future, one can draw on any number of events to continue the narrative.

An analysis of narrative content indicated that impairments were similar across all five content categories (Figures 2 and 5). Notably, neither our patients nor those from the earlier study (57) exhibited any special difficulty in the

production of spatial details (also see 6). Similarly, in another study in which memory-impaired patients imagined scenes (70), the patients produced fewer details in all content categories, both spatial and nonspatial. Note, though, that in a different study from the same group, the number of spatial details was selectively reduced when patients described what might lie outside the boundaries of a photograph (71). In any case, in our patients and in those from the earlier study (57), there was little support for the proposal that the human hippocampus is specifically important for constructing spatially coherent mental images (71). Rather, whatever memory impairments occurred in particular time periods, there was a similar reduction in narrative content across all the content categories that were examined.

Differences in findings among studies of narrative construction could arise for a number of reasons. One possibility is that there might be differences in the methods used to elicit narratives, including differences in experimenter style. For example, McKinlay et al. (78) reviewed the narratives from another study (70) and suggested that impaired scene construction might have as much to do with the nature of the experimenter-patient interaction as with the ability of the patients to imagine scenes. In our Experiment 1, different experimenter methods seem unlikely to explain differences between our findings and those of Race et al. (57). First, we attempted to reproduce their methods as closely as possible. Second, Experiment 1 involved minimal interaction between experimenter and participants (only a request for more information after 3 min). Nevertheless, it is difficult to rule out altogether that some difference in experimenter behavior was

important (such as the quality of the rapport during the test sessions).

Another possibility is that there might be important differences in how narratives are scored. In our Experiment 1, we evaluated the importance of scoring methods by rescoring the transcripts from Race et al. (57) and comparing our results to what was originally reported. The findings were similar, which rules out the importance of scoring methods in this case. In other cases, however, scoring methods can be an important issue. For example, in one study (70), results from an unpublished Spatial Coherence Index suggested that patients had difficulty constructing spatially coherent scenes. However, no indices were used to compare spatial coherence to other features of the narratives (e.g. temporal coherence). Without additional data, it is unclear that the patients had particular difficulty generating spatial details in their narratives.

Lastly, differences in the extent and location of brain damage and in the severity of memory impairment might account for differences in the performance of different groups. Quantitative analysis of magnetic resonance images revealed that our patients (excluding G.P.) had a mean reduction in hippocampal volume of 42.5% and a mean reduction in the volume of the parahippocampal gyrus of 1.0%. In addition, two patients had damage in the basal ganglia (neither of these two patients had the worst score of the group in any time period).

In the earlier study (57), MRI data were reported for four of the eight patients. Of these four, two had damage limited to the MTL, and two had damage that extended into the lateral temporal cortex (MTL+). By our scoring, the number of episodic details per narrative, averaged across time periods, was 15.5 and 6.8

for the MTL and MTL+ patients, respectively. The two MTL patients scored on average one standard deviation below controls, and the two MTL+ patients scored on average 2.4 standard deviations below controls. These data suggest that differences in the severity of retrograde memory impairment between patient groups may arise as a result of differences in the extent of brain lesions. In particular, several studies have demonstrated that when damage extends into the lateral temporal cortex, retrograde amnesia for autobiographical memory affects both recent and remote memory (79-81). In a comprehensive review of studies finding impaired autobiographical memory (82), 54% found that the impairment extended into the remote past. When patients were excluded if they had damage beyond the MTL, 9% of studies found such an extended impairment, and 91% found retrograde amnesia to be temporally graded.

In conclusion, in Experiment 1, our memory-impaired patients and patients from an earlier study (57) produced fewer episodic details than controls. Patients from the earlier study were more impaired than our patients. Patients in both groups had difficulty returning to their narratives after going on tangents, suggesting that anterograde memory impairment may have interfered with narrative construction. In Experiment 2, the experimenter used supportive questioning to help keep participants on task. This procedure rescued the performance of our patients for all time periods except the near past. Notably, neither our patients nor patients from the earlier study exhibited any special difficulty producing spatial details. These findings suggest that medial temporal lobe structures, including the hippocampus, have no special role in constructing

narratives, spatial or nonspatial (except narratives about the recent past), so long as anterograde amnesia does not interfere with performance. The results further suggest that conflicting findings in different patient groups about the status of autobiographical memory likely depend on differences in the locus and extent of brain damage.

## Materials and Methods

### *Participants*

Seven memory-impaired patients participated (Table 1), six with bilateral lesions limited to the hippocampus (CA fields, dentate gyrus, and subicular complex) and one with larger medial temporal lobe lesions. Patients R.S., G.W., and D.A. became amnesic in 1998, 2001, and 2011, respectively, following 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. Patient J.R.W. became amnesic in 1990 following an anoxic episode associated with cardiac arrest. Patients K.E., R.S., J.R.W., L.J., G.W., and D.A. have an average bilateral reduction in hippocampal volume of 49%, 33%, 44%, 46%, 48%, and 35%, respectively (for methods see 28). All values are more than 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 (49), the degree of volume loss in these six patients may reflect nearly complete loss of

hippocampal neurons. The volume of the parahippocampal gyrus (including temporopolar, perirhinal, entorhinal, and parahippocampal cortices) is reduced by 11%, -5%, 12%, -17%, 10%, and -5% for K.E., R.S., J.R.W., L.J., G.W., and D.A., respectively (all values within 2 SDs of the control mean). These values are based on published guidelines for identifying the caudal border of the parahippocampal gyrus (51). The negative values indicate instances where the volume was larger for a patient than for controls.

Patient G.P. has severe memory impairment resulting from viral encephalitis in 1987. G.P. has demonstrated virtually no new learning since the onset of his amnesia, and during repeated testing over many weeks he did not recognize that he had been tested before (52). 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 description of the lesions, can be found in Knutson et al. (53).

Nine healthy volunteers also participated (two females; mean age=60.8 years; mean education = 13.8 years; for patients, mean age = 59.0 years; mean education = 12.8 years). All procedures were approved by the Institutional Review Board at the University of California at San Diego, and participants gave written informed consent prior to participation. All participants completed both Experiments 1 and 2.

*Experiment 1: future imagining and past remembering without experimenter*

*support*

Procedure. Experiment 1 intended to reproduce the methods from an earlier study (57). Participants were asked to recollect 10 specific personal events from the past (e.g. a wedding) and to imagine 10 specific personal events in the future (e.g. winning the lottery). For the past events, five were to be drawn from the last two years (near past), and five were to be drawn from more than 20 years ago (distant past) (>10 years ago for D.A.). For the future events, five were to be from the next two years (near future), and five were to be from more than 20 years in the future (distant future). Data were collected in two sessions. One session asked about distant future events and then near past events, and the other session asked about near future events and then distant past events. The order of the sessions was counterbalanced. For each of 20 recollections, participants were first given a prompt and then asked to describe the event in as much detail as possible (e.g. “Please tell me about your wedding or a wedding that you attended as a young adult. Describe in as much detail as you can what this event was like. Describe where and when the event took place, who was there, how you felt, and what you were thinking.”). The 20 prompts were the same as in Race et al. (57). After the prompt, participants had up to 3 minutes to describe the event without interruption. After 3 minutes, or after a natural ending point, the experimenter provided a single, general probe to elicit additional details (i.e. “Can you tell me any more about where and when the event took place, who was there, how you felt, and what you were thinking?”). Following the general probe, participants were given an additional 3 minutes, again without interruption.

*Race et al. 2011 transcripts*

We obtained transcripts of the narratives collected by Race et al. (57) and independently analyzed them. The analyses described next were carried out for both these data and our own data.

*Narrative scoring*

Narratives were first partitioned into details as has been done previously (40, 55-57). Following Race et al. (57), each detail was then scored as episodic memory, semantic memory, repetition, or metacomment. Episodic details described aspects of specific events. Semantic details described facts that contextualized events. Repetitions were details that repeated information from earlier in the narrative. Metacomments were details that referred to the task itself (e.g. “it’s difficult to remember that”), and were not analyzed further.

Next, each episodic detail was categorized according to its content: event, spatial, time, perceptual, or thought/emotion. Event details described persons or actions. Spatial details described places or spatial relationships between objects or persons. Time details described specific temporal information about an event. Perceptual details described objects, colors, weather, or other sensory information. Thought/emotion details described introspective commentary or internal states. Each semantic detail was also categorized according to its content: general, personal, place, and time. General details described widely known facts. Personal details described facts particular to the participant. Place details described facts about locations. Time details described the broad time period in which events occurred.

Lastly, each detail was scored (1-4) for relevance to the central theme of the narrative (1 = highly relevant, 4 = irrelevant). Relevance ratings made it possible to analyze the effect of tangents on narrative construction. Tangents occur in narratives when the narrative moves off topic from the central event being described. To return to the central event of a narrative after going on a tangent, participants must remember what the central event of the narrative was. Thus, memory-impaired patients might be expected to return from a tangent to the central event less frequently than controls. Tangents were defined as the production of three or more consecutive details that were irrelevant to the central event of the narrative (relevance rating of 4). A participant was said to have returned from a tangent to the central event of the narrative if, following a tangent, he/she produced one or more relevant episodic details before either completing the narrative or receiving the probe from the experimenter.

A.D. was the primary rater for both scoring methods (detail content and relevance). Inter-rater reliability was assessed for each rating method with a second rater blind to group membership. For the content category ratings, the second rater scored a randomly selected 20% of the data from the present study (4 narratives from each participant, 64 narratives). For the relevance ratings, a different second rater, also blind to group membership, scored a randomly selected 20% of the data from both studies (4 narratives from each participant, 140 narratives). Across participants and content ratings, the correlation between raters was .73 and Cronbach's α was .84. For the relevance scores, the correlation between raters was .93 and Cronbach's α was .96. For the Race et al.

(57) narratives, A.D. was blind to group membership during rating and served as the only rater for the content ratings.

*Experiment 2: future imagining and past remembering with experimenter support*

Procedure. Experiments 1 and 2 were separated by at least one year. The procedure was the same as in Experiment 1 with one key difference. In Experiment 2, the experimenter provided support during narrative construction in the form of extensive probing for detail (see 54). New prompts were used to elicit the narratives, and participants could speak for up to five minutes. The probes offered by the experimenter were both general and specific. General probes simply asked for more detail and did not direct the participant in any way. Specific probes oriented participants to types of content (e.g. what time of day was it? How far away will he be from you?). Specific probes sometimes suggested possible content (e.g. was it evening?). Whereas probing in Experiment 1 (and in ref. 57) was limited to a single general probe, in Experiment 2 the experimenter used as many probes as needed to keep the participant on task for five minutes per narrative.

*Narrative scoring*

Narratives were transcribed and partitioned into episodic and semantic details and then categorized by content as described for Experiment 1. A.D. served as the primary rater. Inter-rater reliability was assessed using a blind second rater who did not participate in Experiment 1. The second rater rated a randomly selected 20% of the data (4 events from each participant, 64 events).

Across participants and content ratings, the correlation between raters was .74 and Cronbach's α was .85.

ACKNOWLEDGMENTS

Chapter 3, in full, has been submitted for publication of the material as it may appear in PNAS: USA by Dede, AJO, Wixted, JT, Hopkins RO, Squire, LR. The dissertation author was the primary investigator and author of this paper.

This work was supported by the Medical Research Service of the Department of Veterans Affairs, and NIMH Grant 24600. We thank Jennifer Frascino, Ryan Ward, Reina Mizrahi, Katherine Ann, Christine Smith, Meilinne Hancock, and Soyun Kim for assistance and Elizabeth Race and Mieke Verfaellie for sharing their data.

Table 3.1 Characteristics of Memory-Impaired Patients

| Patient | Age (years) | Education (years) | WAIS-III IQ | WMS-R Attention | Verbal | Visual | General | Delay |
|---|---|---|---|---|---|---|---|---|
| D.A. | 31 | 12 | 90 | 87 | 65 | 95 | 70 | 56 |
| K.E. | 73 | 13.5 | 108 | 114 | 64 | 84 | 72 | 55 |
| L.J. | 77 | 12 | 101 | 105 | 83 | 60 | 69 | <50 |
| R.S. | 58 | 12 | 99 | 99 | 85 | 81 | 82 | <50 |
| G.W. | 55 | 12 | 108 | 105 | 67 | 86 | 70 | <50 |
| J.R.W. | 51 | 12 | 90 | 87 | 65 | 95 | 70 | <50 |
| G.P. | 68 | 16 | 90 | 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 n the normal population with a standard deviation of 15. The WMS-R does not provide numerical scores for individuals who score below 50. IQ scores for R.S. and J.R.W. are from the Wechsler Adult Intelligence Scale-Revised. IQ score for D.A. is from the Wechsler Adult Intelligence Scale-IV.

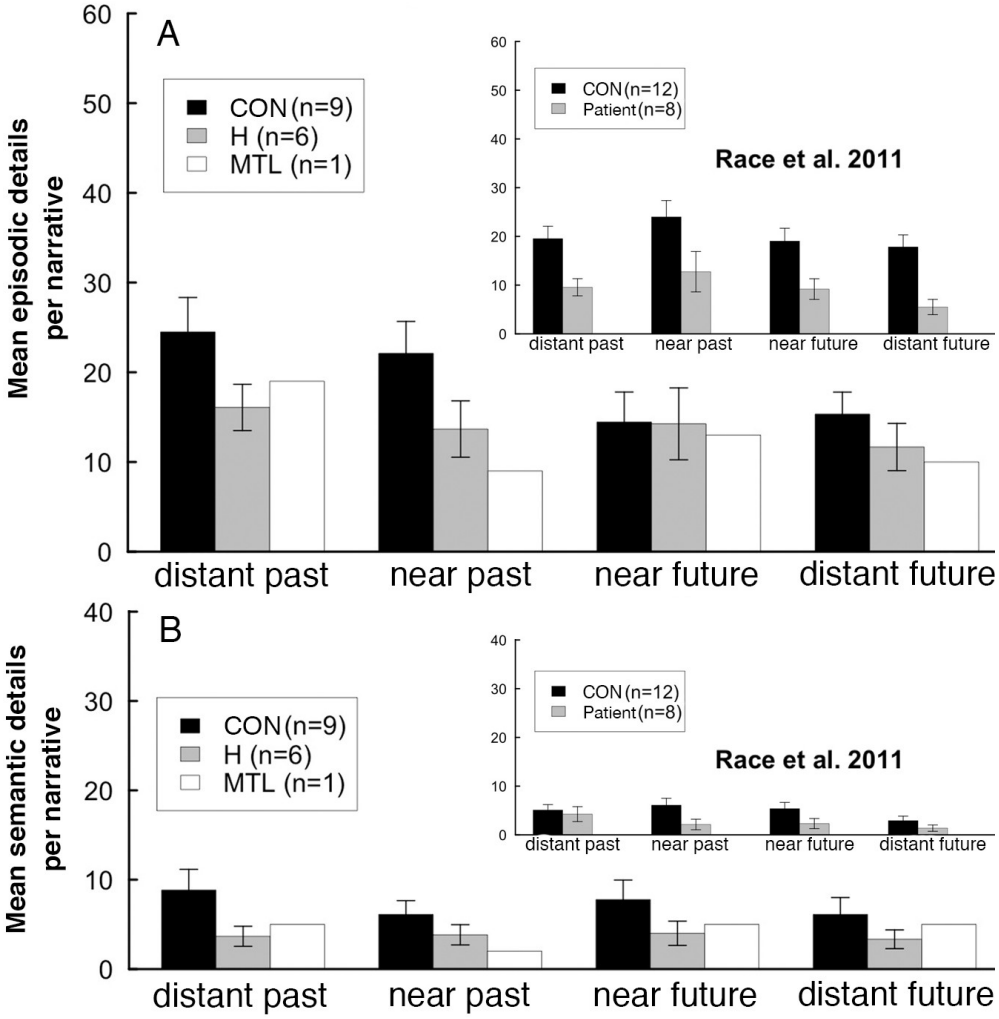


Figure 3.1 Episodic and semantic details per narrative, Exp. 1. Number of episodic (A) and semantic (B) details (Experiment 1). The insets display corresponding findings from our independent analysis of data from Race et al. (2011). CON = control. H = patients with hippocampal lesions. MTL = a patient with large medial temporal lobe lesions. Error bars show standard error of the mean.

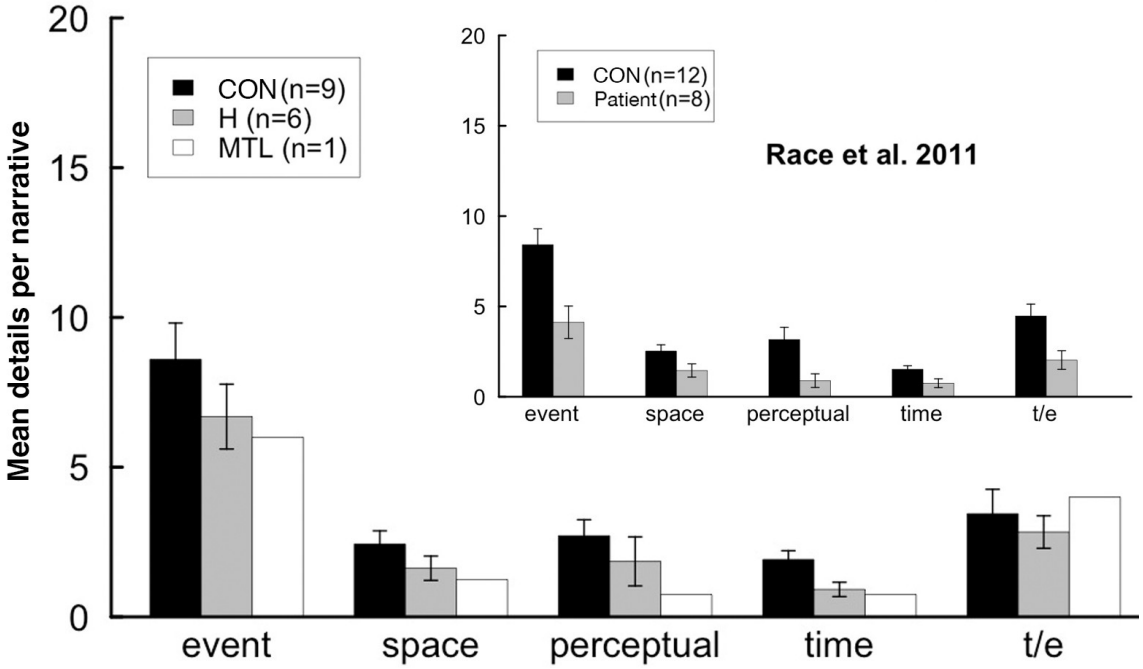


Figure 3.2 Episodic details in each content category, Exp. 1. Number of episodic details per narrative, averaged across time periods (Experiment 1). Details were assigned to one of five categories according to their content. The inset displays corresponding findings from our independent analysis of data from Race et al. (2011). t/e = thought/emotion. CON = control. H = patients with hippocampal lesions. MTL = a patient with large medial temporal lobe lesions. Error bars show standard error of the mean.

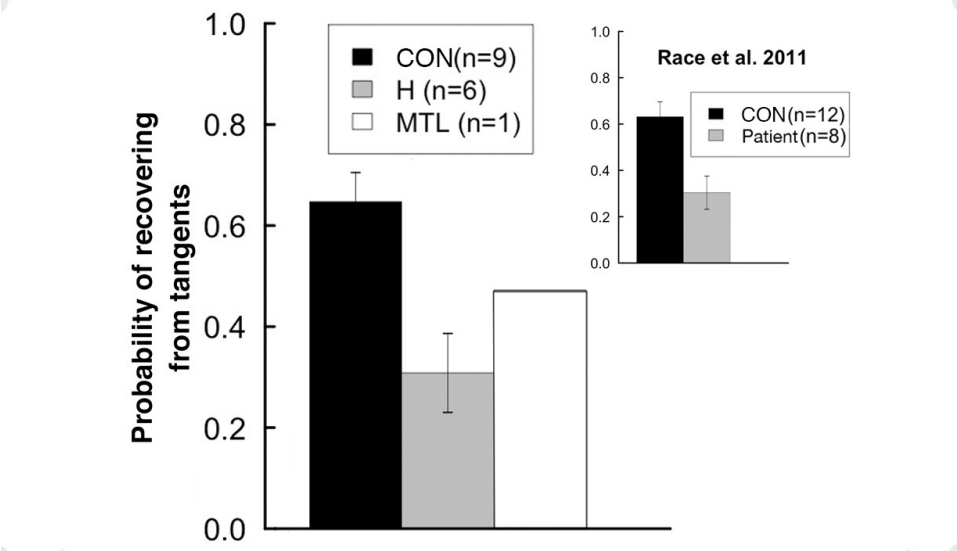


Figure 3.3 Tangent recovery. Tangents were defined as 3 or more consecutive details that were irrelevant to the narrative. Recovery from a tangent was defined as the production of one or more relevant episodic details following the tangent. The inset displays corresponding findings from our independent analysis of data from Race et al. (2011). CON = control. H = patients with hippocampal lesions. MTL = a patient with large medial temporal lobe lesions. Error bars show the standard error of the mean.

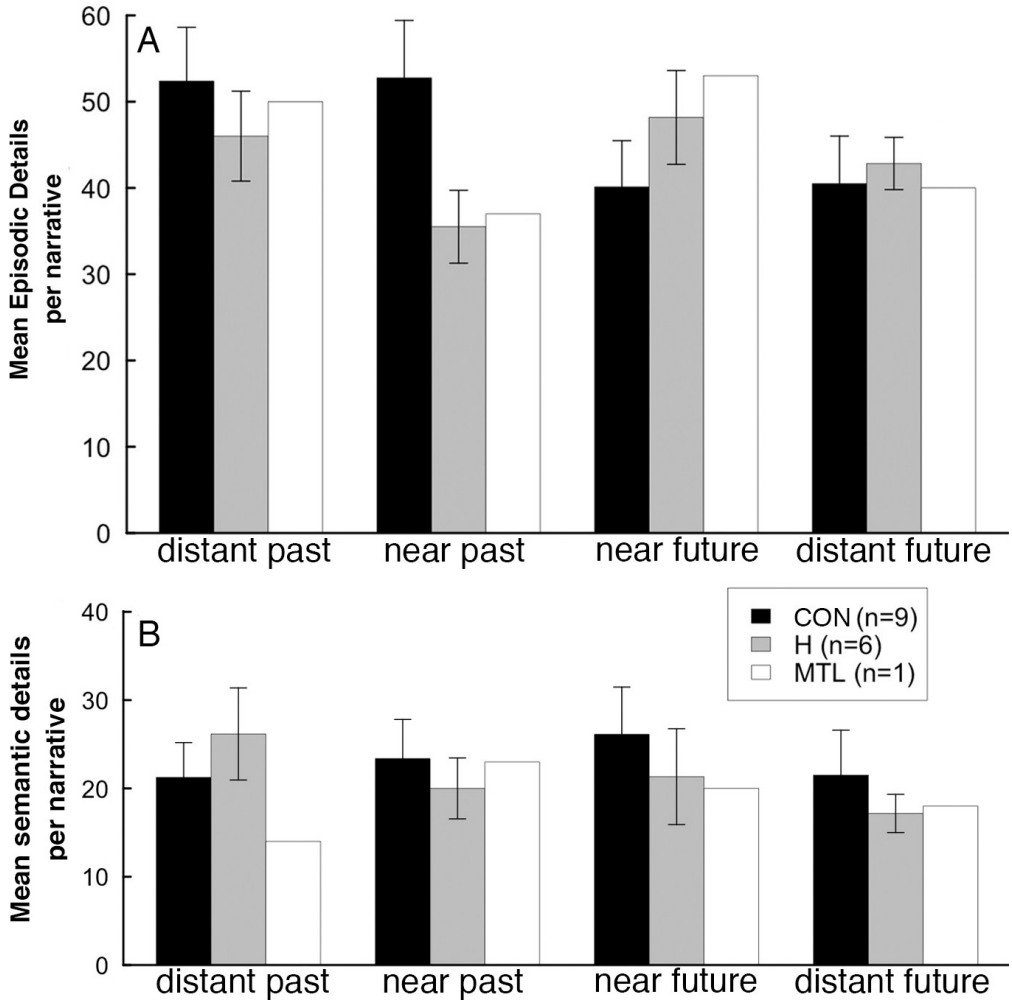


Figure 3.4 Episodic and semantic details per narrative, Exp. 2. Number of episodic (A) and semantic (B) details (Experiment 2). CON = control. H = patients with hippocampal lesions. MTL = a patient with large medial temporal lobe lesions. Error bars show standard error of the mean.

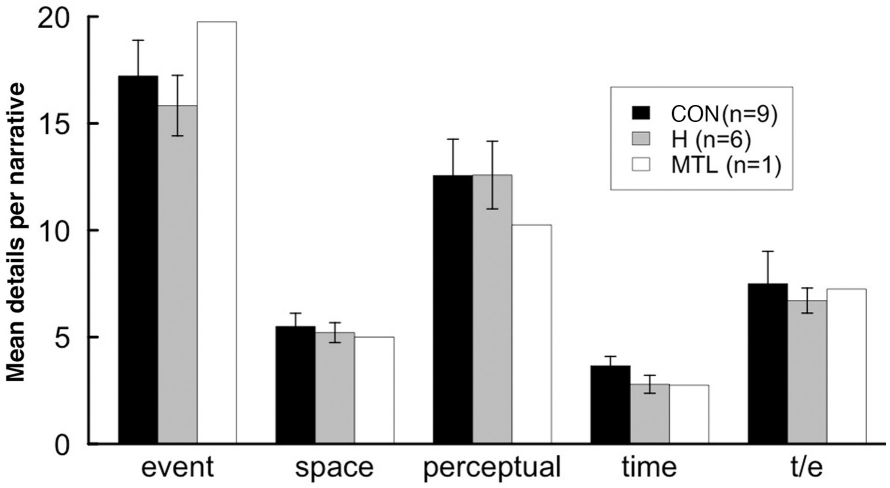


Figure 3.5 Episodic details in each content category, Exp. 2. Number of episodic details per narrative, averaged across time periods (Experiment 2). Details were assigned to one of five categories according to their content. t/e = thought/emotion. CON = control. H = patients with hippocampal lesions. MTL = a patient with large medial temporal lobe lesions. Error bars show standard error of the mean.

# SUMMARY AND CONCLUSION

In three studies patients with damage to the hippocampus were broadly impaired in their ability to recognize words presented during an experiment (Chapter 1). They remembered fewer details than controls about real-world events (Chapter 2). They were able to retrieve detailed and specific memories from their distant past and to imagine detailed and specific events about the future, but they were impaired in their ability to remember events that occurred after the onset of their memory-impairment (Chapter 3). In two respects, patients exhibited disproportionate impairments. First, in Chapter 2, patients were strikingly impaired in their ability to describe real-world events in the order they occurred. Second, in Chapter 3, patients consistently failed to return to the central event of their narratives when going on tangents.

These results demonstrate that patients were broadly impaired for all types of information. There was nothing to suggest a special difficulty for the patients concerning any particular memory process (Chapter 1) or any particular type of content (Chapters 2 and 3). Further, these results demonstrate that when working memory capacity is overloaded, patients with hippocampal damage can exhibit seemingly qualitative changes in performance (Chapter 2). If an association or concept is of sufficient complexity that its initial perception requires more information than can be held within working memory, then it will be impossible to perceive without

long-term memory. Anything that is not perceived cannot be remembered. Thus, patients were able to establish some long-term memory after hippocampal damage (Chapters 1 and 2), but information that exceeded the capacity of working memory was never properly perceived (temporal order in Chapter 2), making it impossible to transfer to long-term memory.

One surprising finding was the immediate role of the hippocampus (Chapters 2 and 3). During the walk (Chapter 2), working memory was continuously overwritten. Thus, in order to link the separate events, working memory representations would have needed to be encoded and immediately retrieved for association with the next event. For narrative construction (Chapter 3), creating a mental event is a continuous and dynamic process. During this process, working memory would have been continuously overwritten. Thus, just as with linking separate real-world events in Chapter 2, long-term memory was necessary to link information generated at different times during narrative construction.

These findings suggest that the hippocampus plays a dynamic role during online processing to link information across perceptual and temporal gaps, and this function may be particularly important when working memory capacity is overloaded. This idea has been considered previously. For example, studies of classical conditioning in memory-impaired patients have demonstrated that the hippocampus is necessary if a gap of as little as 500ms is introduced between the conditioned stimulus and the unconditioned stimulus (84). Neuroimaging has revealed that hippocampal activation associated with subsequent memory for

color-object associations increases with spatiotemporal separation between color and object information (85), and hippocampal activity was highest after, but not during, subsequently remembered events taken from movie clips (86, 87). Using whole-brain magnetoencephalography, it has been suggested that activity immediately following the offset of stimuli may represent replay (88). Indeed, in rats it is common to observe hippocampal cells that engage in offline replay of sequential firing patterns representing recent events, and replay likely facilitates encoding (89, 90, 91, 92, 93). Replay may be particularly important for encoding of temporal sequences by creating the opportunity to retrieve memory of a prior event while experiencing a current event. In this way, it is possible to create associations between two events that occurred at different times. In support of this idea, the firing of hippocampal cells in rats exhibit coding of sequential information (94), and the human hippocampus exhibits heightened activation in association with encoding sequences as opposed to single items (95). In addition, studies in mice have demonstrated that overlapping sets of cells in the hippocampus are responsible for encoding memories formed within close temporal proximity across hours, and manipulating the degree of cell overlap causes predictable changes to associative memory (96).

It may be that hippocampal involvement to bridge temporal gaps is so critical because of the limited capacity of working memory. For example, patients with hippocampal damage exhibit severe deficits on all tasks that exceed the capacity of working memory (50). Studies of both monkeys and humans demonstrate that when tasks are within working memory capacity, stimuli are

represented by relevant perceptual areas in coordination with frontal cortex (97-101). Evidence from neuroimaging and intracranial EEG in humans has demonstrated that the network state of the brain shifts to incorporate the hippocampus as a central node when new memories are encoded and when working memory capacity is exceeded (100, 102-105). Specifically, as working memory load increases, several changes occur in the brain's network state. Hippocampal activation increases. Connectivity between the PFC and the MTL increases. Connectivity between the MTL and lateral temporal cortex increases, and connectivity between PFC and lateral temporal cortex decreases (100, 104, 105). Interestingly, increasing working memory load is also associated with a change from bottom-up to top-down signaling between the MTL and lateral temporal cortex (104). This mechanism appears similar to the top-down signaling observed between these areas during memory retrieval (106), suggesting that the hippocampus may facilitate rehearsal when there is more information to rehearse than can be simultaneously held in working memory.

Considering this dynamic view of hippocampal function aids in the interpretation of seemingly divergent findings from patients with hippocampal damage. For example, Maguire and colleagues studied a patient TT who worked as a London cab driver for 40 years (107). They found that he was able to point accurately to landmarks across London from within a windowless room, and he was intact on several other measures of simple spatial memory for London. He was even able to navigate most routes he was asked to drive in a virtual reality simulation of London. However, he occasionally lost his way such that he never

arrived at his destination. This pattern of results was distinct from that of controls, who were matched for London cab driving experience. Controls would sometimes make errors in their routes but would still eventually arrive at the destination. This finding may be analogous to the failure of patients to return from tangents during narrative construction (Chapter 3). That is, while controls were able to remember where they had made a wrong turn and correct their errors, TT forgot his route entirely after an error had occurred. Thus, TT's occasional failure to arrive at his destination may be interpreted not as evidence for retrograde loss of spatial memory

about London's roadways but as an impact of anterograde amnesia on working memory updating.

In another study, patients with hippocampal damage were tasked with identifying whether a centrally presented abstract stimulus was repeated in a group of 72 simultaneously presented peripheral stimuli (108). Eye tracking data were collected. Patients were impaired at this task, but their impairment was such that their performance was matched with controls when only a small number of fixations intervened between the last viewing of the target stimulus and fixation of a given lure. Thus, the patients' difficulty identifying whether the target stimulus was repeated in the peripheral stimuli was not caused by a perceptual or working memory deficit. Instead, patients were impaired

because without the ability to form a long-term memory representation of the target stimulus, their working memory representation of it was destroyed by interference when a large number of fixations intervened between the last

viewing of the target stimulus and fixation of a given lure.

In summary, patients with hippocampal damage were broadly impaired on tasks of memory. They exhibited no special difficulty with any particular type of content. When working memory capacity is overloaded qualitative changes in performance can occur. These results suggest a dynamic role for the hippocampus in encoding and updating working memory representations during continuous tasks.

REFERENCES

1. Squire LR, Stark CE, Clark RE (2004) The medial temporal lobe. Annu Rev Neurosci 27:279-306.

2. Mandler G (1980) Recognizing - the judgment of previous occurrence. Psychol Rev 87(3):252-271.

3. Diana RA, Reder LM, Arndt J, Park H (2006) Models of recognition: A review of arguments in favor of a dual-process account. Psychon B Rev 13(1):1-21.

4. Reed JM, Squire LR (1997) Impaired recognition memory in patients with lesions limited to the hippocampal formation. Behav Neurosci 111(4):667-675.

5. Eichenbaum H, Yonelinas AP, Ranganath C (2007) The medial temporal lobe and recognition memory. Annu Rev Neurosci 30:123-152.

6. Wixted JT, Squire LR (2011) The medial temporal lobe and the attributes of memory. Trends Cogn Sci 15(5):210-217.

7. Yonelinas AP (1994) Receiver-operating characteristics in recognition memory - evidence for a dual-process model. J Exp Psychol Learn 20(6):1341-1354.

8. Yonelinas AP (1999) The contribution of recollection and familiarity to recognition and source-memory judgments: A formal dual-process model and an analysis of receiver operating characteristics. J Exp Psychol Learn 25(6):1415-1434.

9. Wixted JT (2007) Dual-process theory and signal-detection theory of recognition memory. Psychol Rev 114(1):152-176.

10. Wixted JT, Stretch V (2004) In defense of the signal detection interpretation of remember/know judgments. Psychon B Rev 11(4):616-641.

11. Yonelinas AP, Kroll NEA, Dobbins I, Lazzara M, Knight RT (1998) Recollection and familiarity deficits in amnesia: Convergence of remember-know, process dissociation, and receiver operating characteristic data. Neuropsychology 12(3):323-339.

12. Yonelinas AP (2002) Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. Nature neuroscience 5(11):1236-1241.

13. Wais PE, Wixted JT, Hopkins RO, Squire LR (2006) The hippocampus supports both the recollection and the familiarity components of recognition memory. Neuron 49(3):459-466.

14. Aggleton JP (2005) Sparing of the familiarity component of recognition memory in a patient with hippocampal pathology. Neuropsychologia 43(12):1810-1823.

15. Yonelinas AP, Parks CM (2007) Receiver operating characteristics (ROCs) in recognition memory: a review. Psychol Bull 133(5):800-832.

16. Macmillan NA, Kaplan HL (1985) Detection theory analysis of group data: estimating sensitivity from average hit and false-alarm rates. Psychol Bull 98(1):185-199.

17. Yonelinas AP, Aly M, Wang WC, Koen JD (2010) Recollection and familiarity: examining controversial assumptions and new directions. Hippocampus 20(11):1178-1194.

18. Jang Y, Mickes L, Wixted JT (2012) Three tests and three corrections: comment on Koen and Yonelinas (2010). J Exp Psychol Learn 38(2):513-523.

19. Yonelinas AP (2004) Mild hypoxia disrupts recollection, not familiarity. Cognitive, affective & behavioral neuroscience 4(3):393-400; discussion 401-406.

20. Pearson J, Baden MB, Richter RW (1976) Neuronal depletion in globus pallidus of heroin-addicts. Drug Alcohol Depen 1(5):349-356.

21. Race E, Keane MM, Verfaellie M (2011) Medial temporal lobe damage causes deficits in episodic memory and episodic future thinking not attributable to deficits in narrative construction. J Neurosci 31(28):10262-10269.

22. Barense MD (2012) Intact memory for irrelevant information impairs perception in amnesia. Neuron 75(1):157-167.

23. Wixted JT, Squire LR (2004) Recall and recognition are equally impaired in patients with selective hippocampal damage. Cognitive, affective & behavioral neuroscience 4(1):58-66.

24. Vann SD (2009) Impaired recollection but spared familiarity in patients with extended hippocampal system damage revealed by 3 convergent methods. Proc Natl Acad Sci U S A 106(13):5442-5447.

25. Carlesimo GA (2007) Bilateral damage to the mammillo-thalamic tract impairs recollection but not familiarity in the recognition process: a single case investigation. Neuropsychologia 45(11):2467-2479.

26. Heathcote A (2003) Item recognition memory and the receiver operating characteristic. Journal of experimental psychology. Learning, memory, and cognition 29(6):1210-1230.

27. Jang Y, Wixted JT, Huber DE (2009) Testing signal-detection models of yes/no and two-alternative forced-choice recognition memory. J Exp Psychol Gen 138(2):291-306.

28. Onyper SV, Zhang YX, Howard MW (2010) Some-or-none recollection: Evidence from item and source memory. J Exp Psychol Gen 139(2):341-364.

29. Starns JJ, Ratcliff R (2008) Two dimensions are not better than one: STREAK and the univariate signal detection model of remember/know performance. Journal of memory and language 59(2):169-182.

30. Gold JJ, Squire LR (2005) Quantifying medial temporal lobe damage in memory-impaired patients. Hippocampus 15(1):79-85.

31. RempelClower NL, Zola SM, Squire LR, Amaral DG (1996) Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. J Neurosci 16(16):5233-5255.

32. Franko E, Insausti AM, Artacho-Perula E, Insausti R, Chavoix C (2012) Identification of the human medial temporal lobe regions on magnetic resonance images. Human brain mapping.

33. Bayley PJ, Hopkins RO, Squire LR (2006) The fate of old memories after medial temporal lobe damage. J Neurosci 26(51):13311-13317.

34. Wilson M (1988) MRC psycholinguistic database - machine-usable dictionary, version 2.00. Behavior Research Methods Instruments & Computers 20(1):6-10.

35. Macmillan NA, Creelman CD (2005) Detection Theory, a User's Guide (Lawrence Erlbaum Associates, Inc., Mahwah, NJ).

36. Tulving E (1985) Memory and consciousness. Canadian Psychologist 26:1-12.

37. Rosenbaum RS, et al. (2005) The case of K.C.: contributions of a memory impaired person to memory theory. Neuropsychologia 43(7):989-1021.

38. Kopelman MD & Bright P (2012) On remembering and forgetting our autobiographical pasts: retrograde amnesia and Andrew Mayes's contribution to neuropsychological method. Neuropsychologia 50(13):2961-2972.

39. Moscovitch M, Nadel L, Winocur G, Gilboa A, & Rosenbaum RS (2006) The cognitive neuroscience of remote episodic, semantic and spatial memory. Current Opinion in Neurobiology 16(2):179-190.

40. Bayley PJ, Hopkins RO, & Squire LR (2003) Successful recollection of remote autobiographical memories by amnesic patients with medial temporal lobe lesions. Neuron 37:135-144.

41. Squire LR (1992) Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. Psychol.Rev. 99:195-231.

42. Winocur G & Moscovitch M (2011) Memory transformation and systems consolidation. Journal of the International Neuropsychological Society : JINS 17(5):766-780.

43. Mullally SL, Intraub H, & Maguire EA (2012) Attenuated boundary extension produces a paradoxical memory advantage in amnesic patients. Curr Biol 22(4):261-268.

44. Ranganath C (2010) Binding Items and Contexts: The Cognitive Neuroscience of Episodic Memory. Current Directions in Psychological Science 19(3):131-137.

45. Damasio AR, Eslinger PJ, Damasio H, Van Hoesen GW, & Cornell S (1985) Multimodal amnesic syndrome following bilateral temporal and basal forebrain damage. Arch.Neurol. 42:252-259.

46. Warrington EK & McCarthy RA (1988) The fractionation of retrograde amnesia. Brain Cog. 7:184-200.

47. Bayley PJ, Gold JJ, Hopkins RO, & Squire LR (2005) The neuroanatomy of remote memory. Neuron 46(5):799-810.

48. McCarthy RA, Kopelman MD, & Warrington EK (2005) Remembering and forgetting of semantic knowledge in amnesia: a 16-year follow-up investigation of RFR. Neuropsychologia 43(3):356-372.

49. Rempel-Clower NL, Zola SM, Squire LR, & Amaral DG (1996) Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. The Journal of neuroscience 16(16):5233-5255.

50. Jeneson A & Squire LR (2012) Working memory, long-term memory, and medial temporal lobe function. Learning & Memory 19(1):15-25.

51. Franko E, Insausti AM, Artacho-Perula E, Insausti R, & Chavoix C (2014) Identification of the human medial temporal lobe regions on magnetic resonance images. Human brain mapping 35(1):248-256.

52. Bayley PJ, Frascino JC, & Squire LR (2005) Robust habit learning in the absence of awareness and independent of the medial temporal lobe. Nature 436(7050):550-553.

53. Knutson AR, Hopkins RO, & Squire LR (2013) A pencil rescues impaired performance on a visual discrimination task in patients with medial temporal lobe lesions. Learning & Memory 20(11):607-610.

54. Kirwan CB, Bayley PJ, Galvan VV, & Squire LR (2008) Detailed recollection of remote autobiographical memory after damage to the medial temporal lobe. Proc Natl Acad Sci U S A 105(7):2676-2680.

55. Levine B, Svoboda E, Hay JF, Winocur G, & Moscovitch M (2002) Aging and autobiographical memory: dissociating episodic from semantic retrieval. Journal of Psychology and Aging 17:677-689.

56. Hassabis D, Kumaran D, Vann SD, & Maguire EA (2007) Patients with hippocampal amnesia cannot imagine new experiences. Proc Natl Acad Sci U S A 104(5):1726-1731.

57. Race E, Keane MM, & Verfaellie M (2011) Medial temporal lobe damage causes deficits in episodic memory and episodic future thinking not attributable to deficits in narrative construction. The Journal of neuroscience 31(28):10262-10269.

58. Tulving E (1983) Elements of Episodic Memory (Oxford University Press).

59. Tulving E (2002) Episodic memory: from mind to brain. Annu Rev Psychol 53: 1-25.

60. Squire LR (1992) Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 99(2): 195-231.

61. Kirwan CB, Galvan VV, Bayley PB, Squire LR (2008) Detailed recollection of remote autobiographical memory after damage to the medial temporal lobe. Proc Natl Acad Sci U S A 105(7): 2676-2680.

62. Squire LR, van der Horst AS, McDuff SGR, Frascino JC, Hopkins RO, Mauldin KN (2010) Role of the hippocampus in remembering the past and imagining the future. Proc Natl Acad Sci U S A 107(44): 19044-19048.

63. Kopelman MD, Bright P (2012) On remembering and forgetting our autobiographical pasts: retrograde amnesia and Andrew Mayes's contribution to neuropsychological method. Neuropsychologia 50(13): 2961-2972.

64. Moscovitch M, Nadel L, Winocur G, Gilboa A, Rosenbaum, SR (2006) The cognitive neuroscience of remote episodic, semantic and spatial memory. Current Opinion in Neurobiology 16: 179-190.

65. Winocur G, Moscovitch M (2011) Memory transformation and systems consolidation. J Int Neuropsychol Soc 17(5): 766-780.

66. Rosenbaum RS, Moscovitch M, Foster JK, Schnyer DM, Gao F, Kovacevic N, Verfaellie M, Black SE, Levine B (2008) Patterns of autobiographical memory loss in medial-temporal lobe amnesic patients. J Cogn Neurosci 20(8): 1490-1506.

67. Tulving E (1985) Memory and consciousness. Canadian Psycol 26(1): 1-12.

68. Shacter DL, Addis DR, Buckner RL (2007) Remembering the past to imagine the future: the prospective brain. Nature Rev Neurosci 8: 657-661.

69. Buckner RL, Carroll DC (2007) Self-projection and the brain. Trends Cogn Sci 11(2): 49-57.

70. Hassabis D, Kumaran D, Vann, SD, Maguire, EA (2007) Patients with hippocampal amnesia cannot imagine new experiences. Proc Natl Acad Sci U S A 104(5): 1726-1731.

71. Mullally SL, Intraub H, Maguire EA (2012) Attenuated boundary extension produces a paradoxical memory advantage in amnesic patients. Curr Biol 22(4): 261-268.

72. Zola-Morgan S, Cohen NJ, Squire LR (1983) Recall of remote episodic memory in amnesia. Neuropsychologia 21(5): 487-500.

73. Rosenbaum RS, Gilboa A, Levine B, Winocur G, Moscovitch M (2009) Amnesia as an impairment of detail generation and binding: evidence from personal, fictional, and semantic narratives in K.C. Neuropsychologia 47: 2181-2187.

74. Zeman AZJ, Beschin N, Dewar M, Della Sala S (2013) Imagining the present: amnesia may impair descriptions of the present as well as of the future and the past. Cortex 49: 637-645.

75. Caspari I, Parkinson SR (2000) Effects of memory impairment on discourse. J Neurolinguistics 13: 15-36.

76. Bayley PJ, Hopkins RO, Squire LR (2003) Successful recollection of remote autobiographical memories by amnesic patients with medial temporal lobe lesions. Neuron 38(1): 135-144.

77. Addis DR, Schacter DL (2012) The hippocampus and imagining the future: where do we stand? Front Hum Neurosci 5(173): 1-15.

78. McKinlay A, McVittie C, Della Sala S (2010) Imagining the future: does a qualitative analysis add to the picture? J Neuropsychology 4: 1-13.

79. Bright P, Buckman J, Fradera A, Yoshimasu H, Colchester ACF, Kopelman MD (2006) Retrograde amnesia in patients with hippocampal, medial temporal, temporal lobe, or frontal pathology. Learning & Memory 13: 545-557.

80. Bayley PJ, Gold JJ, Hopkins RO, Squire LR (2005) The neuroanatomy of remote memory. Neuron 46: 799-810.

81. Bayley PJ, Hopkins RO, Squire LR (2007) The fate of old memories after medial temporal lobe damage. J Neuroscience 26(51): 13311-13317.

82. Lah S, Miller L (2008) Effects of temporal lobe lesions on retrograde memory: a critical review. Neuropsychol Rev 18(1): 24-52.

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

84. Clark RE, Squire LR (1998). Classical conditioning and brain systems: the

role of awareness. Science 280(5360):77-81.

85. Staresina BP, Davachi L (2009). Mind the gap: binding experiences across space and time in the human hippocampus. Neuron 63(2):267-76.

86. Hasson U, Furman O, Clark D, Dudai Y, Davachi L (2008). Enhanced intersubject correlations during movie viewing correlate with successful episodic encoding. Neuron 57(3):452-62.

87. Ben-Yakov A, Dudai Y (2011). Constructing realistic engrams: poststimulus activity of hippocampus and dorsal striatum predicts subsequent episodic memory. J Neurosci 31(24):9032-42.

88. Fuentemilla L, Penny WD, Cashdollar N, Bunzeck N, Duzel E (2010) Theta-coupled periodic replay in working memory. Curr Biol 20(7):606-12.

89. Buzsaki G (1989). Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 31(3):551-70.

90. Buzsaki G (1996). The hippocampo-neocortical dialogue. Cereb Cortex 6(2):81-92.

91. Skaggs WE, McNaughton BL (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. Science 271(5257):1870-3.

92. Carr MF, Jadhav SP, Frank LM (2011). Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. Nat Neurosci. 14(2):147-53.

93. Nakashiba T, Buhl DL, McHugh TJ, Tonegawa S (2009). Hippocampal CA3 output is crucial for ripple-associated reactivation and consolidation of memory. Neuron 62(6):781-7.

94. Allan TA, Salz DM, McKenzie S, Fortin NJ (2016). Nonspatial sequence coding in CA1 neurons. J Neurosci 36(5):1547-63.

95. Tubridy S, Davachi L (2011) Medial temporal lobe contributions to episodic sequence encoding. Cereb Cortex 21(2):272-80.

96. Silva AJ, Zhou Y, Rogerson T, Shobe J, Balaji J (2009). Molecular and cellular approaches to memory allocation in neural circuits. Science

326(5951):391-5.

97. Fuster JM, Alexander GE (1971). Neuron activity related to short-term memory. Science 173(3997):652-4.

98. Bauer RH, Fuster JM (1976). Delayed-matching and delated-response deficit from cooling dorsolateral prefrontal cortex in monkeys. J Comparative and Physiological Psych 90(3):293-302.

99. Serences JT, Ester E, Vogel E, Awh E (2009). Stimulus-specific delay activity in human primary visual cortex. Psych Science 20(2):207-14.

100. Rissman J, Gazzaley A, D'Esposito M (2008). Dynamic adjustments in prefrontal, hippocampal, and inferior temporal interactions with increasing visual working memory load. Cereb Cortex 18(7):1618-29.

101. Gregoriou GG, Rossi AF, Ungerleider LG, Desimone R (2014). Lesions of prefrontal cortex reduce attentional modulation of neuronal responses and synchrony in V4. Nat Neurosci 17(7):1003-11.

102. Ranganath C, Cohen MS, Brozinksy CJ (2005). Working memory maintenance contributes to long-term memory formation: neural and behavioral evidence. Cognitive Neuroscience 17(7):994-1010.

103. Ranganath C, Heller A, Cohen MS, Brozinsky CJ, Rissman J (2005). Functional connectivity with the hippocampus during successful memory formation. Hippocampus 15(8):997-1005.

104. Axmacher N, Elger CE, Fell J (2008) Ripples in the medial temporal lobe are relevant for human memory consolidation. Brain 131(7):1806-17.

105. Axmacher N, Mormann F, Fernandez G, Cohen MX, Elger CE, Fell J (2007) Sustained neural activity patterns during working memory in the human medial temporal lobe. J Neurosci 27(29):7807-16.

106. Takeda M, Koyano KW, Hirabayashi T, Adachi Y, Miyashita Y (2015). Top-down regulation of laminar circuit via inter-area signal for successful object memory recall in monkey temporal cortex. Neuron
86(3):840-52.

107. Maguire EA, Nannery R, Spiers HJ (2006). Navigation around London by a taxi driver with bilateral hippocampal lesions. Brain 129(11):2894-907.

108. Warren DE, Duff MC, Tranel D, Cohen NJ (2011). Observing degradation of

visual representations over short intervals when medial temporal lobe is damaged. Cognitive Neuroscience 23(12):3862-73.