

Recognition Memory and the Human Hippocampus

Joseph R. Manns,^{1,6} Ramona O. Hopkins,^{2,3}
Jonathan M. Reed,⁴ Erin G. Kitchener,¹
and Larry R. Squire^{1,5,*}

¹University of California, San Diego
La Jolla, California 92093

²Brigham Young University
Provo, Utah 84602

³LDS Hospital
Salt Lake City, Utah 84143

⁴East Carolina University
Greenville, North Carolina 27858

⁵Veterans Affairs Medical Center
San Diego, California 92161

Summary

The capacity for declarative memory depends on the hippocampal region and adjacent cortex within the medial temporal lobe. One of the most widely studied examples of declarative memory is the capacity to recognize recently encountered material as familiar, but uncertainty remains about whether intact recognition memory depends on the hippocampal region itself and, if so, what the nature of the hippocampal contribution might be. Seven patients with bilateral damage thought to be limited primarily to the hippocampal region were impaired on three standard tests of recognition memory. In addition, the patients were impaired to a similar extent at Remembering and Knowing, measures of the two processes thought to support recognition performance: the ability to remember the learning episode (episodic recollection) and the capacity for judging items as familiar (familiarity).

Introduction

The formation of declarative memory depends on a system of anatomically related structures in the medial temporal lobe (the hippocampal region, which includes the hippocampus, dentate gyrus, and subicular complex, and the adjacent perirhinal, entorhinal, and parahippocampal cortices) (Squire and Zola-Morgan, 1991; Eichbaum and Cohen, 2001). In humans, declarative memory supports the capacity to recollect facts and events and can be contrasted with a collection of nondeclarative memory abilities: habits and skills, simple forms of conditioning, and other ways that the effects of experience can be expressed through performance rather than recollection (Squire, 1992; Schacter and Tulving, 1994). One of the most widely studied examples of declarative memory is recognition memory, the capacity to judge a recently encountered item as familiar. The capacity for recognition memory has been particularly well documented in mice, rats, and monkeys, as well as in humans.

Recognition memory is widely viewed as consisting

of two components, a recollective (episodic) component that supports the ability to remember the episode in which an item was encountered and a familiarity component that supports the ability to know that an item was presented, but without providing memory of the episode itself (Mandler, 1980; Tulving, 1985; Yonelinas, 2002). An important question concerns whether the brain structures that comprise the medial temporal lobe memory system differ in their contributions to recognition memory or differ in how they support its recollective and familiarity components.

One view has been that recognition memory is supported by the cortical areas along the parahippocampal gyrus (for example, the perirhinal cortex) and that the hippocampus itself is needed only for more complex tasks of declarative memory such as forming associations and conjunctions among stimuli (Aggleton and Shaw, 1996; Vargha-Khadem et al., 1997; Tulving and Markowitsch, 1998). Good recognition performance has been described following restricted hippocampal lesions in a case of developmental amnesia (patient Jon; Vargha-Khadem et al., 1997; Baddeley et al., 2001) and in one patient with adult-onset amnesia (patient Y.R.; Mayes et al., 2002). However, other patients with damage restricted primarily to the hippocampal region are impaired at tasks of recognition memory (Hopkins et al., 1995b; Reed and Squire, 1997; Manns and Squire, 1999; Stark and Squire, 2001; Stark et al., 2002).

A second view has been that the hippocampus is essential for normal recognition memory but that the hippocampus itself supports only the recollective (episodic) component of recognition. By this view, judgments based on familiarity can be supported by adjacent cortex in the medial temporal lobe or perhaps by other structures important for nondeclarative memory (Yonelinas et al., 1998; Eldridge et al., 2000; Brown and Aggleton, 2001; Verfaellie and Keane, 2002; Yonelinas, 2002). It has been difficult to test this proposal because the distinction between recollection and familiarity cannot readily be investigated in experimental animals and because, even in humans, there are a limited number of methods for reliably separating judgments based on recollection from judgments based on familiarity. In the Remembering and Knowing paradigm (Tulving, 1985), individuals first study a list of items and then at test make two different judgments about a series of old and new items. They first judge whether they have previously encountered an item and then decide whether they “remember” the item (because the item evokes a recollection of having encountered it as part of the study episode) or whether they simply “know” that the item is familiar but have no specific memory of having encountered it. This is an intuitive and straightforward distinction, as illustrated by the common experience of confidently recognizing (Knowing) that someone is familiar but without remembering who the person is and without remembering any episode in which the person was previously encountered.

Studies of memory-impaired patients with the Remember and Know procedure have been interpreted

*Correspondence: lsquire@ucsd.edu

⁶Present address: Boston University, Boston, Massachusetts 02215.

Table 1. Characteristics of Amnesic Patients

Patient	Age	Education	WAIS-III	WMS-R				
	(years)	(years)	IQ	Attention	Verbal	Visual	General	Delay
J.S.	36	14	90	92	85	63	81	75
J.R.W.	38	12	90	87	65	95	70	<50
G.W.	42	12	108	105	67	86	70	<50
R.S.	45	12	99	99	85	81	82	<50
M.J.	61	16	139	125	62	93	62	<50
L.J.	64	12	101	105	83	60	69	<50
A.B.	64	20	107	87	62	72	54	<50

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

as showing that both Remembering and Knowing are impaired but that the impairment in Knowing might be less severe than the impairment in Remembering (Yonelinas et al., 1998, 2002; Yonelinas, 2002; but see Knowlton and Squire, 1995). However, these studies all involved mixed groups of patients, patients without radiological information, or patients with damage to both the hippocampus and the parahippocampal gyrus. Accordingly, the studies to date do not address the question of whether damage limited to the hippocampus might in fact spare the capacity to experience familiarity.

The present study was designed to resolve the question of whether the human hippocampus is important for recognition memory and, if so, whether it is important only for recollection or for both recollection and the experience of familiarity. In Experiment 1, we tested seven patients with bilateral damage thought to be limited primarily to the hippocampal region (Table 1, Figure 1) on three standard tests of recognition memory. In Experiment 2, we used the Remember and Know procedure to assess the relative ability of these patients to make recognition judgments based on recollection and familiarity. The patients were impaired on all three recognition tests and had similarly severe impairments in both recollective memory and in familiarity.

Results

Experiment 1: Standard Recognition Memory Tests

Figure 2 shows the performance of amnesic patients with damage limited primarily to the hippocampal region and controls on three tests of recognition memory. One patient (J.S.) took only the third test (Figure 2C). The second and third tests (Figures 2B and 2C) include recall portions, and the recall data are presented as well. The amnesic patients exhibited impaired recognition memory performance on all the tests (recognition memory of words after 24 hr, $t[11] = 3.87$; $p < 0.01$; recognition memory of faces after 24 hr, $t[11] = 2.64$; $p < 0.05$; recognition portion of the Doors and People Test, $t[10] = 2.38$; $p < 0.05$; each of the five recognition trials of the Rey Auditory Learning Test, RAVLT, $ts[13] > 2.15$; all $ps \leq 0.05$). Recall performance on the RAVLT was also impaired on each trial ($ps < 0.01$). On the recall portion of the Doors and People Test, the patients were impaired, but their score did not reach significance ($t[10] = 1.23$, $p > 0.10$).

To consider the possibility that recognition memory might be impaired to a lesser extent than recall in the patients, we compared recall and recognition memory on the Doors and People Test and on the RAVLT. For the Doors and People Test, none of the patients performed more than 15 percentile points higher on the recognition portion than on the recall portion. In addition, a percentile score can be calculated that reflects the difference between a participant's recall performance and recognition performance (<50th percentile indicates relatively better recognition performance, and >50th percentile indicates relatively better recall performance). The patients and controls obtained almost identical percentile scores on this measure (30.5 ± 6.7 and 30.6 ± 5.7 , respectively). For the RAVLT, the scores obtained by the patients were converted to Z scores based on the mean and standard deviation of the control scores. All the patients obtained poorer recognition scores than recall scores. Thus, no patient showed a pattern of results on either the Doors and People Test or on the RAVLT that would suggest that recall was impaired more than recognition.

Experiment 2: Recollective and Familiarity Components of Recognition Memory

The impaired recognition memory performance of the patients with hippocampal damage could have been due to a global impairment in recognition memory or to an impairment in only the component of recognition memory that reflects recollective (episodic) memory. Experiment 2 addressed this issue by asking participants not only to judge whether they had encountered each item previously but also to judge whether their recognition judgment was based on recollection (Remembering) or simple familiarity (Knowing). For each test item, participants first judged whether the item had been encountered before (yes/no) and then gave a Remember or Know response for the items judged to be repeated.

Figure 3 shows overall recognition memory performance (d') for the patients with hippocampal damage and two control groups. The data were collapsed across all eight recognition memory tests (four verbal tests and four nonverbal tests) and across items given Remember judgments and items given Know judgments. The patients performed worse than controls tested at the same 10–20 min study-test delay (mean $d' \pm SEM = 0.68 \pm 0.08$ and 1.67 ± 0.51 for the patients and controls, re-

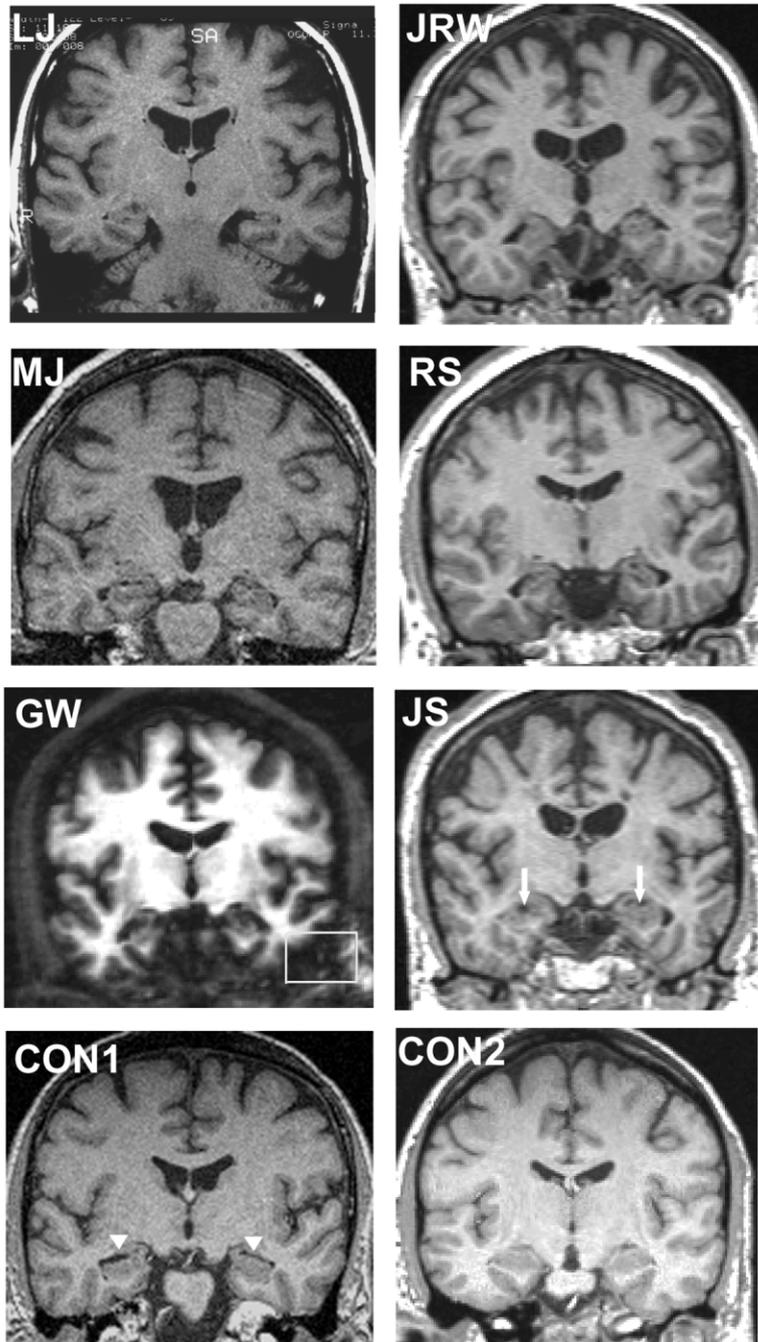


Figure 1. Magnetic Resonance Images for Six Amnesic Patients with Damage Limited Primarily to the Hippocampal Region and Two Healthy Controls

The images are T1-weighted coronal sections at the level of the anterior hippocampus. CON1 and CON2 are controls, aged 56 years and 35 years, respectively. The left side of the brain is on the right side of the image (radiologic view). For five of the patients, the volume of the hippocampal region relative to intracranial volume is reduced by an average of 30% (see text). For patient J.S., the hippocampus was not reduced in volume but had several focal lesions (indicated by white arrows). White triangles on the image for CON1 indicate the hippocampal region. An imaging artifact is visible in the area of the left lateral temporal lobe in the image of patient G.W. (box).

spectively; $t[24] = 4.91$, $p < 0.01$) and similarly to controls tested after 1 week (mean $d' \pm SEM = 0.64 \pm 0.10$). All three groups had a similar tendency to endorse test items as ones that had been encountered previously ($0.43 \pm .02$, $0.50 \pm .04$, and $0.46 \pm .08$, for controls tested after 10–20 min, controls tested after 1 week, and patients, respectively).

Figure 4 shows recognition memory performance (d') on all eight tests (four verbal and four nonverbal) for items given Remember judgments and for items given Know judgments (two scoring methods). The patients performed worse than the controls (CON) for items given Remember judgments (mean $d' \pm SEM = 0.72 \pm 0.14$

and 1.80 ± 0.16 for patients and controls, respectively; $t[24] = 3.96$, $p < 0.01$) and also for items given Know judgments, regardless of the method of calculation (see Data Analysis; for the first method, 0.17 ± 0.13 and 0.59 ± 0.11 ; $t[24] = 2.10$, $p < 0.05$; for an alternate method that assumes independence between Remembering and Knowing, 0.45 ± 0.07 and 1.13 ± 0.10 ; $t[24] = 3.98$, $p < 0.01$). For Remember responses, the score of the patients averaged 60% lower than the control score. For Know responses, the patient score was 71% lower (standard method) or 60% lower (alternate method) than the control score. Despite their impairment, the patients did score above chance levels for Remember responses

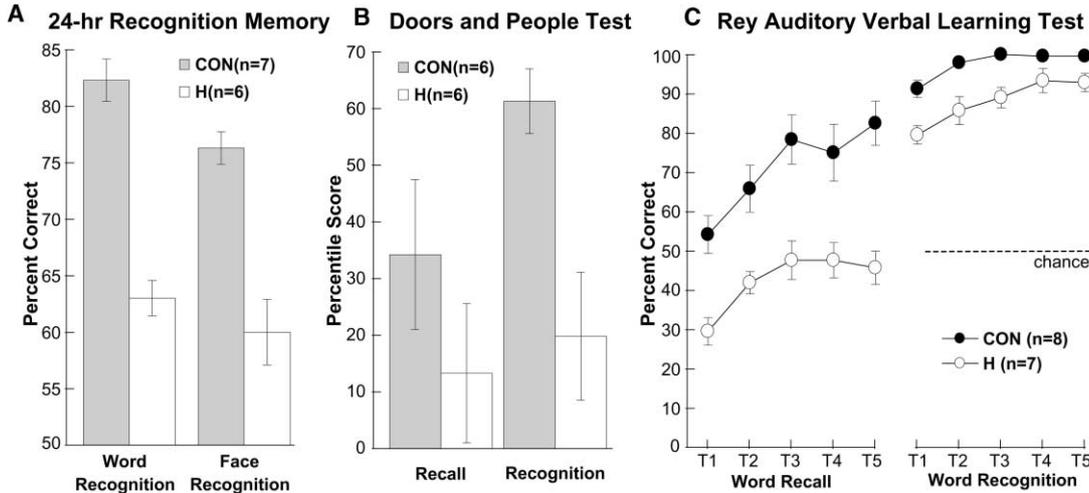


Figure 2. Performance on Three Standard Recognition Memory Tests for Patients with Damage Limited to the Hippocampal Region and Controls

(A) A version of the Warrington (1984) recognition memory test for words and faces in which the study-test delay was 24 hr

(B) Doors and People Test (Baddeley et al., 1994)

(C) Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964)

T1–T5 denote trials 1–5. One patient (J.S.) participated in only the RAVLT. The Doors and People Test and the RAVLT include recall portions, and the recall data are shown here as well. H indicates patients with hippocampal damage; CON indicates controls. Brackets indicate standard error of the mean.

($p < .01$) and for Ind-Know responses ($p < .01$), though not for Know responses ($p > 0.10$).

The data were also reanalyzed without patient A.B., who was ineligible for MRI (and for whom only the results of a CT scan were available). The remaining six patients

performed worse than controls for items given Remember judgments (mean patient $d' = 0.78 \pm 0.14$; $t[23] = 3.49$, $p < .01$), for items given Know judgments as analyzed by the alternate method (Ind-Know, 0.50 ± 0.07 ; $t[23] = 3.48$, $p < .01$), and also for items given Know judgments analyzed by the first method (0.20 ± 0.15 ; $t[23] = 1.81$, $p = .08$).

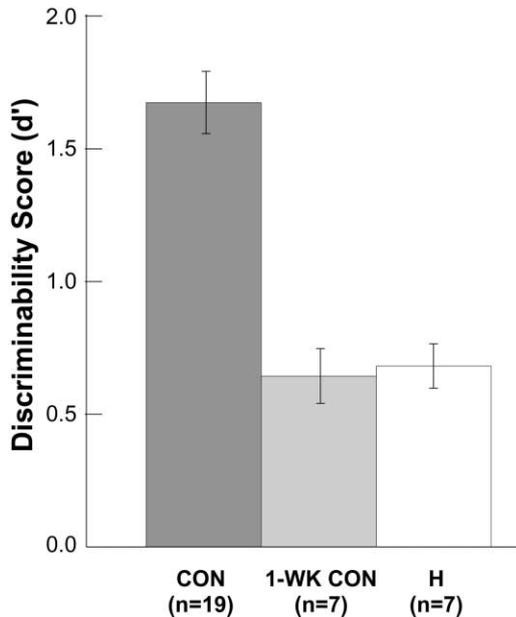


Figure 3. Discriminability Scores, Expressed as d' , for Patients with Damage Limited Primarily to the Hippocampal Region and Controls. Participants took eight different recognition memory tests (four verbal and four nonverbal). A second control group (1-WK CON) was tested after a week instead of 10–20 min. H indicates patients with hippocampal damage; CON indicates controls. Brackets indicate standard error of the mean.

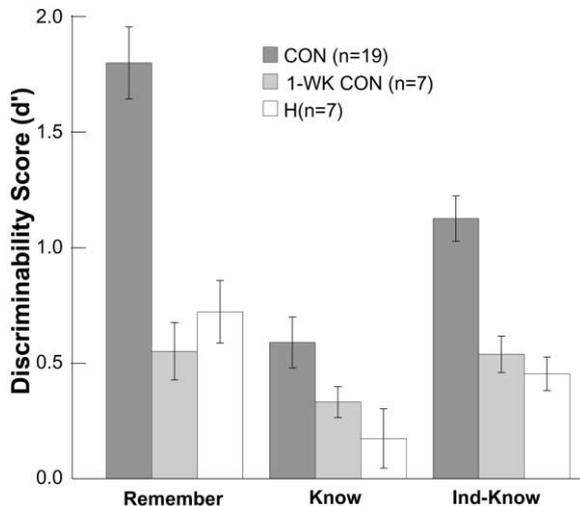


Figure 4. Discriminability Scores, Expressed as d' , for Patients with Damage Limited Primarily to the Hippocampal Region and Controls. The scores are shown separately for items given Remember judgments (Remember), for items given Know judgments (Know), and for items given Know judgments analyzed by an alternate method that assumes that Remembering and Knowing are independent processes (Ind-Know, see text). A second control group (1-WK CON) was tested after a week. H indicates patients with hippocampal damage; CON indicates controls. Brackets indicate standard error of the mean.

Table 2. Mean Hit Rates and False Alarm Rates for Experiment 2

Group	Overall		Remember		Know		Ind-Know	
	HR	FAR	HR	FAR	HR	FAR	HR	FAR
CON	.70 ± .03	.16 ± .03	.44 ± .04	.05 ± .01	.25 ± .03	.11 ± .02	.43 ± .04	.12 ± .02
1-WK CON	.62 ± .04	.38 ± .05	.26 ± .06	.13 ± .04	.37 ± .04	.26 ± .33	.49 ± .04	.30 ± .04
H	.53 ± .08	.30 ± .07	.35 ± .07	.16 ± .04	.22 ± .02	.19 ± .04	.38 ± .07	.24 ± .06

The hit rate (HR) is the frequency with which a repeated item was correctly identified as having been encountered at study. The false alarm rate (FAR) is the frequency with which a new item was incorrectly identified as having been encountered at study. The HR and FAR for items given know judgments were also recalculated based on a formula that assumes independence between remembering and knowing (Ind-Know; see Experimental Procedures). Note that the mean discriminability (d') scores reported in the text and depicted in Figures 3 and 4 were obtained by averaging each participant's d' score within each group rather than by using the HR and FAR group means shown here. Accordingly d' scores calculated from the data in this Table will vary slightly from the d' scores in the test and figures. Error values indicate SEM.

To examine further how the impairment in Knowing exhibited by the patients compared to their impairment in Remembering, a control group was tested after a 1 week delay to approximate the overall performance of the patients (Figure 3). The scores obtained by controls tested after a week were similar to the scores obtained by the patients. Thus, there was no indication in the data that Know responses were relatively spared by hippocampal damage (Figure 4). If anything, the results were in the direction of Know responses being more impaired than Remember responses. That is, in the case of Remember responses, the patients performed slightly better than the delayed control group, but in the case of Know responses the patients performed slightly worse.

Table 2 shows the hit rate and false alarm rate for all items, for items given Remember judgments and for items given Know judgments. The hit rate and false alarm rate for items given Know judgments were also calculated based on a formula (see Experimental Procedures) that assumes independence between Remembering and Knowing.

For the patients and their 19 controls, we also examined the data separately for the four verbal tests and the four nonverbal tests. The patients performed worse than the controls for the verbal tests (mean $d' \pm$ SEM for Remember responses, Know responses, and Know responses analyzed with the alternate method = 0.83 ± 0.19 , 0.24 ± 0.29 , 0.53 ± 0.20 and 2.19 ± 0.18 , 0.64 ± 0.12 , 1.46 ± 0.15 for patients and controls, respectively) and for the nonverbal tests (0.73 ± 0.12 , 0.20 ± 0.11 , 0.47 ± 0.09 and 1.44 ± 0.14 , 0.62 ± 0.12 , 1.02 ± 0.10 for patients and controls, respectively). T tests between patients and controls were statistically significant ($p < 0.05$). The one exception was that, for the verbal material, Know responses analyzed with the standard method did not reach significance ($t[24] = 1.49$, $p > 0.10$). This lack of statistical significance appeared to result from one patient having an extreme bias to identify verbal items as being new, a bias known to produce artificially high d' scores when calculated using the standard method (Donaldson, 1996). When the alternate method (Ind-Know) was used to obtain the d' score for the verbal material, the difference between patients and controls for Knowing was significant ($t[24] = 3.28$, $p < 0.01$).

Discussion

Seven patients with bilateral damage thought to be limited primarily to the hippocampal region were impaired

on three standard tests of recognition memory (Experiment 1). In addition, the patients were similarly impaired on the recollective (episodic) and familiarity components of recognition memory (Experiment 2). Specifically, the percent reduction in the performance of the patients was similar across the measures that were obtained for recollection and familiarity. Moreover, when controls were tested after a long delay (1 week) so that the recollective component of recognition performance (their Remember score) was as poor as that of the patients, the controls also matched the patients with respect to the familiarity component of recognition performance (their Know score). These findings show that intact recognition memory depends on the integrity of the hippocampal region. Further, the importance of the hippocampal region encompasses the capacity to make judgments based on familiarity as well as the capacity to make judgments based on recollection.

It is not possible to determine whether the residual (above chance) recognition memory performance observed in the patients for Remembering responses as well as for Knowing responses (Ind-Know) is supported by remaining tissue within the hippocampal region or by adjacent cortical structures in the medial temporal lobe. The results of Experiment 2 suggest that the hippocampal region is ordinarily important for both Remembering and Knowing. Accordingly, if the hippocampal region in the patients retains any functional integrity, it would likely participate along with the adjacent cortex in supporting both Remembering and Knowing.

It is relevant, of course, how well the Remember and Know procedure can separate the hypothetical processes of recollection and familiarity. The dimensions of interest (recollection/familiarity and Remember/Know) are ultimately based on subjective criteria, and the Remember and Know procedure itself depends on how reliably participants can make the subjective judgments. It has also been argued that yes-no response bias can influence the assessment of Knowing unless measures are used to reduce the impact of these factors, for example, by using the Ind-Know procedure for assessing Knowing or by allowing for "guess" responses in addition to Remember and Know judgments (Donaldson, 1996; Gardiner et al., 2002). Note, however, that the Know scores of the patients in this study were extremely low and no better than the Remember scores. Thus, unless Know responses fail altogether to index familiarity, the findings count strongly against the idea that the

capacity for familiarity is independent of hippocampal function.

One might also propose that the Remember and Know procedure does not reliably index qualitatively different recognition processes but may under some conditions simply reflect relatively strong memory and high familiarity on the one hand (Remember responses) and relatively weak memory and low familiarity on the other (Know responses) (Donaldson, 1996). Under some views (Yonelinas, 2002), when individuals respond in this manner, the assumptions underlying standard Remember/Know analyses are invalid because all responses, being based on familiarity, should be given Know responses. If all participants responded in this manner, then the appropriate way to ask about the capacity for familiarity judgments in the patients is to compare the overall recognition performance of patients and controls (Figure 3; $d' = 0.68$ versus 1.67 , $t[24] = 4.9$, $p < .001$). If only the patients responded in this manner, then the appropriate comparison is between the overall recognition performance of the patients and Know performance of the controls ($d' = 0.68$ versus 1.13 , using the estimate of Know for performance [Ind-Know], which corrects for the fact that the standard method underestimates the frequency of Know responses, $t[24] = 2.62$, $p < .02$). Thus, whatever approach is used, there is no evidence that the capacity for familiarity is independent of hippocampal function.

The interpretation of the present findings also depends critically on how confidently the impairment in recognition performance can be attributed to damage within the hippocampal region. Because hypoxia can result in global cerebral atrophy (Grubb et al., 2000; Hopkins et al., 1995a), one must evaluate the anatomical data carefully. Detailed neurohistological analysis has documented that a limited period of ischemia can produce selective damage in the hippocampal region (Zola-Morgan et al., 1986). In addition, patients with hypoxic damage who were identified on the basis of MRI to have damage limited primarily to the hippocampal region were subsequently found on the basis of detailed neurohistological analysis to have hippocampal damage consistent with the MRI findings (Rempel-Clower et al., 1996). While neurohistological data provide the most unambiguous evidence about the nature of damage, the quantitative MRI data for the patients in the current study suggest that they have selective damage to the hippocampal region.

The findings for recognition memory in Experiment 1 confirm in a group of patients with hippocampal damage what has been reported previously for a smaller number of patients with histologically confirmed lesions within the hippocampus (patient R.B., Zola-Morgan et al., 1986; patient G.D., Rempel-Clower et al., 1996) and patients with histologically confirmed lesions of the hippocampus together with some neuronal loss in entorhinal cortex (patients W.H. and L.M., Rempel-Clower et al., 1996). A possible exception to this pattern of data for adult-onset amnesia is Y.R. (Mayes et al., 2002), a patient with radiological evidence of restricted hippocampal damage. Y.R. was given 43 recognition memory tests, and she performed normally or nearly normally on some of the tests. Yet, when her performance was assessed across all 43 tests by calculating Z scores, her average Z score (-0.5) was significantly below average control

performance (Z score of 0). This impairment was considered to be modest and less severe than her impairment in recall (mean Z score across 34 free recall tests = -3.6). On the basis of these findings, it was proposed that Y.R.'s capacity to make familiarity judgments was intact (Holdstock et al., 2002). Yet, Y.R. was impaired on the visual paired-comparison task, which measures the spontaneous tendency to look at novel pictures instead of familiar pictures and which would appear to involve the discrimination of familiarity. Thus, Y.R. might have simply a milder form of the memory impairment exhibited by our study patients. Alternatively, because Y.R. scored poorly on recall and was reported to have at least as much hippocampal damage as our patients (46% volume reduction), it is possible that the locus of damage within the hippocampal region is different for Y.R. than for most of our patients.

Recognition performance was also found to be distinctly better than recall performance in a patient (Jon) with restricted hippocampal damage that occurred perinatally (Baddeley et al., 2001; Vargha-Khadem et al., 2001). Jon's good recognition performance was proposed to depend on his ability to make judgments based on familiarity, following from the observation that he could not be taught the Remember/Know distinction and appeared to lack the ability to recall the contextual detail necessary for making Remember responses (Baddeley et al., 2001). The authors raised the possibility that this pattern of findings might be limited to cases of developmental amnesia, where there is a possibility of functional reorganization during development and the opportunity to acquire alternative learning strategies.

Studies of human memory using functional magnetic imaging (fMRI) have sometimes found greater activity in the hippocampal region during associative or recollective recognition (for example, in association with Remember judgments) than in tasks more likely to depend on relative familiarity, such as tasks involving Know judgments (Henke et al., 1999; Eldridge et al., 2000; Yonelinas et al., 2001). However, the increased activity in the hippocampal region in these studies was matched by an increase in activity in the parahippocampal gyrus, so that these studies do not speak to the separate contribution of the hippocampal region itself. In addition, it is evident that hippocampal activity is often not observed during standard recognition tasks, for example, in contrasts between old items and new items (Yonelinas et al., 2001), because of elevated activity associated with encoding the unfamiliar new items (Stark and Squire, 2000). When this contribution to hippocampal activity is accommodated in the experimental design, robust and selective activation can be observed in the hippocampal region during conventional tasks of recognition memory (Stark and Squire, 2000, 2001). A final difficulty in interpreting findings of increased activity when recognition memory tasks are more elaborate (for example, when a task involves Remember judgments rather than Know judgments) is that such findings may reflect differences in the amount of information being retrieved or differences in retrieval effort rather than qualitative differences between kinds of recognition. Distinguishing qualitative from quantitative differences will likely require evidence for opposite effects in different brain regions (double dissociations).

Our finding that the hippocampus is essential for normal recognition performance and important for judgments of both recollection and familiarity does not speak against the importance of the recollection-familiarity distinction itself. One kind of evidence favoring this distinction comes from fMRI studies and studies of event-related potentials (ERPs), which suggest that the capacity to recollect episodic information about recently encountered material and the capacity to experience familiarity for the material depend on different neural substrates (Smith, 1993; Rugg et al., 1998; Henson et al., 1999; Curran, 2000). While concerns have been raised that the effects attributed to the conscious experience of familiarity might be related instead to perceptual or conceptual priming (Olichney et al., 2000), fMRI and ERPs hold promise for clarifying the relationship between recollection and familiarity.

One possibility is that familiarity depends on the integrity of structures within the medial temporal lobe, including the hippocampal region, and that episodic recollection depends on these same structures and also on the frontal lobes (Shimamura and Squire, 1987; Davidson and Glisky, 2002). Patients with frontal lobe damage and elderly individuals with neuropsychological signs of frontal lobe dysfunction are impaired at recollecting episodic information about past events (for example, temporal order information and other information about the source of remembered material) (Schacter, 1987; Janowsky et al., 1989; Milner et al., 1991; Parkin and Walter, 1992; Kesner et al., 1994; Kopelman et al., 1997).

The nature of recognition memory and the importance of the hippocampus and adjacent cortex have been studied extensively in experimental animals, and the matter is still a topic of some debate. In the monkey, recognition memory has typically been found to be impaired by restricted hippocampal lesions (Beason-Held et al., 1999; Zola et al., 2000; but see Murray and Mishkin, 1998), though deficits also occur after damage to perirhinal cortex (Mishkin and Murray, 1994; Buffalo et al., 1999). Studies in the rodent have yielded mixed results and different interpretations (Mumby, 2001; Broadbent et al., 2002), perhaps because rodents readily adopt nondeclarative (nonhippocampal) strategies to solve problems that humans perform declaratively (Reed and Squire, 1999). One view is that recognition memory is typically impaired in rats if the retention delay is sufficiently long and the hippocampal lesions sufficiently large (see Clark et al., 2001). In one recent study, recognition performance in rats with intrahippocampal injections of APV was intact after a delay of 5 min but impaired after a delay of 15 min (Baker and Kim, 2002; for another finding of nearly normal performance in rats with hippocampal lesions after a 5 min delay, see Mumby et al., 2002). Finally, mice lacking the NMDAR-1 subunit in the CA1 region of the hippocampus were impaired at a task of novel object recognition at delays of 30 min and longer (the visual paired-comparison task) (Rampon et al., 2000).

Single-cell recordings in humans and experimental animals also suggest a role for the hippocampus in recognition memory performance. For example, neurons recorded from the hippocampus during visual or olfactory recognition tasks can convey stimulus-specific information as well as an abstract match-nonmatch signal—that is, a response that signals the outcome of

the recognition process rather than a signal about the stimulus itself (Fried et al., 1997; Wood et al., 1999; Suzuki and Eichenbaum, 2000).

It perhaps should not be surprising that recognition memory, including the component of recognition memory that supports familiarity judgments, depends on the integrity of the hippocampus. The hippocampus is the final stage of convergence within the medial temporal lobe, receiving input from both the perirhinal and parahippocampal cortices, as well as the entorhinal cortex. The entorhinal cortex receives about two-thirds of its cortical input from the perirhinal and parahippocampal cortices and originates the major cortical projections to the hippocampus (Suzuki and Amaral, 1994). Anatomical considerations alone suggest that the hippocampus is positioned to combine and extend the operations of memory formation that are carried out by the more specialized structures that project to it. Further, the physiological data are consistent with the idea that the hippocampus carries out a more abstract, less stimulus-specific operation than the adjacent cortex that projects to it (Suzuki and Eichenbaum, 2000). We suggest that all these operations, the more stimulus-specific operations in the adjacent cortex and the more abstract operations in the hippocampus, make essential contributions to recognition memory. As a result, none of the components of recognition memory will be intact unless all these medial temporal lobe structures are functioning. In addition, we suggest that sharp dichotomies such as associative versus nonassociative memory, episodic versus semantic memory, and recollection versus familiarity do not adequately describe the division of labor between the hippocampus and adjacent cortex. Further study, guided by neuroanatomy, can be expected to improve the description of ways in which these regions make different contributions to some aspects of memory functions (see for example, Fernandez et al., 2002; Davachi and Wagner, 2002).

Experimental Procedures

Participants

Seven amnesic patients (six men and one woman) with damage limited primarily to the hippocampal region (CA fields, dentate gyrus, and subicular complex) participated in both experiments (Table 1). All the patients had a moderately severe memory impairment. Their scores for copy and delayed (12 min) reproduction of the Rey-Osterrieth figure (Osterrieth, 1944; maximum score = 36) were 29.1 and 4.1, respectively (controls = 30.3 and 20.6; Squire et al., 1989). On immediate and delayed recall of a short prose passage (Gilbert et al., 1968), they recalled 5.3 and 1.0 segments, respectively (controls = 7.4 and 5.8).

Patients A.B. and J.R.W. became amnesic after an anoxic episode associated with cardiac arrest (in 1976 for A.B. and 1990 for J.R.W.). G.W. and R.S. became amnesic following a drug (heroin) overdose and associated respiratory failure (in 2001 for G.W. and 1998 for R.S.). J.S. became amnesic in 1999 following carbon monoxide poisoning. L.J. became amnesic during a 6 month period that began in 1988 with no known precipitating event. Her memory impairment has remained stable since that time. M.J. had a 10 year history of cardiovascular disease. On June 6, 1996, he awoke from a night's sleep complaining of memory difficulties. His memory impairment has remained stable since that time.

For six of the seven patients, bilateral hippocampal damage was quantified by magnetic resonance imaging (MRI) in a 1.5T clinical scanner (Figure 1). The volume of the full anterior-posterior length of the hippocampus, as well as the volume of the parahippocampal

gyrus and the lateral temporal cortex, was measured using criteria based on histological analysis of healthy brains (Amaral and Insausti, 1990; Insausti et al., 1998). For each patient, the hippocampal and parahippocampal gyrus volumes were divided by the intracranial volume to correct for brain size (for L.J., only areal measurements based on coronal sections were available). Relative to age- and gender-matched healthy controls (3 to 4 for each patient), J.R.W., G.W., R.S., M.J., and L.J. have an average bilateral reduction in hippocampal size of 29%, 45%, 40%, 10%, and 28%, respectively. For J.S., the hippocampus was not reduced in volume but focal lesions were present (see Figure 1). In comparison, for all patients, the size of the parahippocampal gyrus was within normal limits (mean = 2%, range = -15% to +15%). The seventh patient (A.B.) is unable to participate in magnetic resonance imaging studies but is thought to have hippocampal damage on the basis of etiology (anoxia) and a neurologic examination indicating well-circumscribed amnesia. In addition, high-resolution computed tomography (CT) images obtained in 2001 were consistent with restricted damage to the hippocampal region (Schmolck et al., 2002).

Control data for Experiment 1 were taken from published reports (24 Hour Words and Faces Test and Rey Auditory Verbal Learning Test, Squire and Shimamura, 1986; Doors and People Test, Manns and Squire, 1999). These 14 healthy individuals (7 men and 7 women) averaged 57.3 years of age and 14.8 years of education. Twenty-six controls (19 men and 7 women) were tested in Experiment 2. They averaged 59.9 ± 2.8 years of age (patients = 50.0 ± 4.7) and 14.9 ± 0.5 years of education (patients = 13.9 ± 1.2).

Procedure: Experiment 1

24 Hour Words and Faces Recognition Memory Test

Participants were shown 50 common words one at a time or 50 black and white photographs of faces one at a time. For each item, participants made a pleasant/nonpleasant judgment. Twenty-four hours later, participants took a two-alternative forced-choice recognition memory test (modified from Warrington, 1984).

Doors and People Test

Participants were given the four subtests of the Doors and People Test according to the published manual (Baddeley et al., 1994): a verbal recall test, a visual recall test, a verbal recognition memory test, and a visual recognition memory test.

Rey Auditory Verbal Learning Test

For the recall portion of the Rey Auditory Verbal Learning Test (RAVLT), 15 words were presented orally, and then recall was tested. The study-test sequence was then repeated four times. The recognition portion of the test used 15 different words. Five successive study-test trials were given, and testing on each trial followed a yes-no format with 30 words (15 old, 15 new).

Procedure: Experiment 2

Amnesic patients ($n = 7$) and controls ($n = 19$) were given four verbal and four nonverbal recognition memory tests (two tests during each of four sessions). In each session, participants first studied nonverbal material (on two occasions, 36 black and white photographs of faces, and on two occasions, 36 black and white abstract line drawings) and also studied verbal material (36 common words, 4 to 6 letters in length). After a 10 min delay, participants took a yes-no recognition memory test for the verbal material (36 old items and 36 new items) and then a similar test for the nonverbal material (36 old items and 36 new items). Thus, the study-test delay for the nonverbal material was about 20 min. For each test item, participants first made a yes-no judgment and then made a Remember-Know judgment if an item had been endorsed.

During the 10 min delay between the verbal study and verbal test of each session, the distinction between Remembering and Knowing was explained using established instructions (Gardiner and Parkin, 1990; Knowlton and Squire, 1995). Thus, the participants were instructed:

“A Remember response is rather like answering the question ‘What was the name of the last television program you saw?’ You are likely to remember not only the name of the program, but also such specific details as whom you saw it with, where you saw it, and whether you had a snack during the program. A Know response is more like meeting someone on the street

whom you are certain you know without being aware of where you know that person from. You are sure you know him, but don’t remember any other details about him, such as his name or where you met.”

All participants were able to explain the distinction appropriately in their own words before testing and were able to provide meaningful justifications when asked why they gave items either Remember or Know judgments (participants were prompted to explain their response for the first Remember and first Know response on each test). A card that summarized the instructions remained in view during the test phases.

To approximate the overall recognition memory performance of the amnesic patients, seven controls took the same tests but with a retention interval of 1 week rather than 10–20 min.

Data Analysis for Experiment 2

Recognition memory performance was assessed with a discriminability score (d') (Green and Swets, 1966), which measures how well participants could discriminate between studied items and new items. We calculated a d' score for Know judgments in two different ways, as discussed previously (Yonelinas et al., 1998). The results were the same with both methods.

By the first, more traditional method, the d' score for Remembering was determined from the hit rate for items given Remember judgments and the false alarm rate for items given Remember judgments. The d' score for Knowing was determined from the hit rate for items given Know judgments and the false alarm rate for items given Know judgments.

The second method of calculating d' scores for Remember and Know judgments is based on the assumption that Remember and Know judgments are independent. This second method is arguably more sound than the first method in that it recognizes (and corrects for) the fact that Know responses are underestimated by the traditional method because a proportion of the items given Remember responses could have been given Know responses as well (Yonelinas et al., 2002). By the second method, the hit rate (HR) and false alarm rate (FAR) for Knowing are calculated as follows: $HR = HR_{(Know)}/(1 - HR_{(Remember)})$; $FAR = FAR_{(Know)}/(1 - FAR_{(Remember)})$.

Acknowledgments

Supported by the Medical Research Service of the Department of Veterans Affairs, NIMH Grant 24600, and the Metropolitan Life Foundation. We thank James Moore, Joyce Zouzounis, Jennifer Frascino, and Leah Swalley for their assistance and John Wixted for helpful discussion.

Received: August 2, 2002

Revised: November 18, 2002

References

- Aggleton, J.P., and Shaw, C. (1996). Amnesia and recognition memory: a re-analysis of psychometric data. *Neuropsychologia* 34, 51–62.
- Amaral, D.G., and Insausti, R. (1990). Hippocampal formation. In *The Human Nervous System*, G. Paxinos, ed. (San Diego, CA: Academic Press), pp. 711–755.
- Baddeley, A.D., Emslie, H., and Nimmo-Smith, I. (1994). The Doors and People Test: A Test of Visual and Verbal Recall and Recognition (Bury St. Edmunds: Thames Valley Test Co.).
- Baddeley, A., Vargha-Khadem, F., and Mishkin, M. (2001). Preserved recognition in a case of developmental amnesia: implications for the acquisition of semantic memory? *J. Cogn. Neurosci.* 13, 357–369.
- Baker, K.B., and Kim, J.J. (2002). Effects of stress and hippocampal NMDA receptor antagonism on recognition memory in rats. *Learn. Mem.* 9, 58–65.
- Beason-Held, L.L., Rosene, D.L., Killiany, R.J., and Moss, M.B. (1999). Hippocampal formation lesions produce memory impairment in the rhesus monkey. *Hippocampus* 9, 562–574.
- Broadbent, N., Clark, R.E., Zola, S., and Squire, L.R. (2002). The

- medial temporal lobe and memory. In *The Neuropsychology of Memory*, second edition, L.R. Squire and D. Schacter, eds. (New York: Guilford Press), pp. 3–23.
- Brown, M.W., and Aggleton, J.P. (2001). Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nat. Rev. Neurosci.* 2, 51–61.
- Buffalo, E.A., Ramus, S.J., Clark, R.E., Teng, E., Squire, L.R., and Zola, S.M. (1999). Dissociation between the effects of damage to perirhinal cortex and area TE. *Learn. Mem.* 6, 572–599.
- Clark, R.E., West, A.N., Zola, S.M., and Squire, L.R. (2001). Rats with lesions of the hippocampus are impaired on the delayed nonmatching-to-sample task. *Hippocampus* 11, 176–186.
- Curran, T. (2000). Brain potentials of recollection and familiarity. *Mem. Cognit.* 28, 923–938.
- Davachi, L., and Wagner, A.D. (2002). Hippocampal contributions to episodic encoding: insights from relational and item-based learning. *J. Neurophysiol.* 88, 982–990.
- Davidson, P.S.R., and Glisky, E.L. (2002). Neuropsychological correlates of recollection and familiarity in normal aging. *Cogn. Affect. Behav. Neurosci.* 2, 174–186.
- Donaldson, W. (1996). The role of decision processes in remembering and knowing. *Mem. Cognit.* 28, 523–533.
- Eichenbaum, H., and Cohen, N.J. (2001). *From Conditioning to Conscious Recollection: Memory Systems of the Brain*. (New York: Oxford University Press).
- Eldridge, L.L., Knowlton, B.J., Furmanski, C.S., Bookheimer, S.Y., and Engel, S.A. (2000). Remembering episodes: a selective role for the hippocampus during retrieval. *Nat. Neurosci.* 3, 1149–1152.
- Fernandez, G., Klaver, P., Fell, J., Grunwald, T., and Elger, C.E. (2002). Human declarative memory formation: segregating rhinal and hippocampal contributions. *Hippocampus* 12, 514–519.
- Fried, I., MacDonald, K.A., and Wilson, C.L. (1997). Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron* 18, 753–765.
- Gardiner, J.M., and Parkin, A.J. (1990). Attention and recollective experience in recognition memory. *Mem. Cognit.* 18, 579–583.
- Gardiner, J.M., Ramponi, C., and Richardson-Klavehn, A. (2002). Recognition memory and decision processes: a meta-analysis of remember, know, and guess responses. *Memory* 2, 83–98.
- Gilbert, J., Levee, R., and Catalano, K. (1968). A preliminary report on a new memory scale. *Percept. Mot. Skills* 27, 277–278.
- Green, D.M., and Swets, J.A. (1966). *Signal Detection Theory and Psychophysics* (New York: Wiley).
- Grubb, N.R., Fox, K.A., Smith, K., Best, J., Blane, A., Ebmeier, K.P., Glabus, M.F., and O'Carroll, R.E. (2000). Memory impairment in out-of-hospital cardiac arrest survivors is associated with global reduction in brain volume, not focal hippocampal injury. *Stroke* 31, 1509–1514.
- Henke, K., Buck, A., Weber, B., and Wieser, H.G. (1999). Human hippocampus establishes associations in memory. *Hippocampus* 7, 249–256.
- Henson, R.N., Rugg, M.D., Shallice, T., Josephs, O., and Dolan, R.J. (1999). Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *J. Neurosci.* 19, 3962–3972.
- Holdstock, J.S., Mayes, A.R., Roberts, N., Cezayirli, E., Isaac, C.L., O'Reilly, R.C., and Norman, K.A. (2002). Under what conditions is recognition spared relative to recall after selective hippocampal damage in humans? *Hippocampus* 12, 341–351.
- Hopkins, R.O., Gale, S.D., Johnson, S.C., Anderson, C.V., Bigler, E.D., Blatter, D.D., and Weaver, L.K. (1995a). Severe anoxia with and without concomitant brain atrophy and neuropsychological impairments. *J. Int. Neuropsychol. Soc.* 1, 501–509.
- Hopkins, R.O., Kesner, R.P., and Goldstein, M. (1995b). Item and order recognition memory in subjects with hypoxic brain injury. *Brain Cogn.* 27, 180–201.
- Insausti, R., Juottonen, K., Soininen, H., Insausti, A.M., Partanen, K., Vainio, P., Laakso, M.P., and Pitkanen, A. (1998). MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *AJNR Am. J. Neuroradiol.* 19, 659–671.
- Janowsky, J.S., Shimamura, A.P., and Squire, L.R. (1989). Source memory impairment in patients with frontal lobe lesions. *Neuropsychologia* 27, 1043–1056.
- Kesner, R.P., Hopkins, R.O., and Fineman, B. (1994). Item and order dissociation in humans with prefrontal cortex damage. *Neuropsychologia* 32, 881–891.
- Knowlton, B.J., and Squire, L.R. (1995). Remembering and knowing: two different expressions of declarative memory. *J. Exp. Psychol. Learn. Mem. Cogn.* 21, 699–710.
- Kopelman, M.D., Kinglsey, D., and Stanhope, N. (1997). Temporal and spatial context memory in patients with focal frontal, temporal lobe, and diencephalic lesions. *Neuropsychologia* 35, 1533–1545.
- Mandler, G. (1980). Recognizing: the judgment of previous occurrence. *Psychol. Rev.* 87, 252–271.
- Manns, J.R., and Squire, L.R. (1999). Impaired recognition memory on the Doors and People test after damage limited to the hippocampal region. *Hippocampus* 9, 495–499.
- Mayes, A.R., Holdstock, J.S., Isaac, C.L., Hunkin, N.M., and Roberts, N. (2002). Relative sparing of item recognition memory in a patient with adult-onset damage limited to the hippocampus. *Hippocampus* 12, 325–340.
- Milner, B., Corsi, P., and Leonard, G. (1991). Frontal-lobe contribution to recency judgements. *Neuropsychologia* 29, 601–618.
- Mishkin, M., and Murray, E.A. (1994). Stimulus recognition. *Curr. Opin. Neurobiol.* 4, 200–206.
- Mumby, D.G. (2001). Perspectives on object-recognition memory following hippocampal damage: lessons from studies in rats. *Behav. Brain Res.* 127, 159–181.
- Mumby, D.G., Gaskin, S., Glenn, M.J., Schramek, T.E., and Lehmann, H. (2002). Hippocampal damage and exploratory preferences in rats: memory for objects, places, and contexts. *Learn. Mem.* 9, 49–57.
- Murray, E.A., and Mishkin, M. (1998). Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. *J. Neurosci.* 18, 6568–6582.
- Olichney, J.M., Van Petten, C., Paller, K.A., Salmon, D.P., Iragui, V.J., and Kutas, M. (2000). Word repetition in amnesia. Electrophysiological measures of impaired and spared memory. *Brain* 123, 1948–1963.
- Osterrieth, P.A. (1944). Le test de copie d'une figure complexe. *Archives de Psychologie* 30, 206–356.
- Parkin, A.J., and Walter, B.M. (1992). Recollective experience, normal aging, and frontal dysfunction. *Psychol. Aging* 7, 290–298.
- Rampon, C., Ya-Ping, T., Goodhouse, J., Shimizu, E., Kyin, M., and Tsien, J.Z. (2000). Enrichment induces structural changes and recovery from nonspatial memory deficits in CA1 NMDAR1-knockout mice. *Nat. Neurosci.* 3, 238–244.
- Reed, J.M., and Squire, L.R. (1997). Impaired recognition memory in patients with lesions limited to the hippocampal formation. *Behav. Neurosci.* 111, 667–675.
- Reed, J.M., and Squire, L.R. (1999). Impaired transverse patterning in human amnesia is a special case of impaired memory for two-choice discrimination tasks. *Behav. Neurosci.* 113, 411–419.
- Rempel-Clower, N., Zola, S.M., Squire, L.R., and Amaral, D.G. (1996). Three cases of enduring memory impairment following bilateral damage limited to the hippocampal formation. *J. Neurosci.* 16, 5233–5255.
- Rey, A. (1964). *L'Examen Clinique Psychologie [The Clinical Exam in Psychology]* (Paris: Presses Universitaires de France).
- Rugg, M.D., Mark, R.E., Walla, P., Schloerscheidt, A.M., Birch, C.S., and Allan, K. (1998). Dissociation of the neural correlates of implicit and explicit memory. *Nature* 392, 595–598.
- Schacter, D.L. (1987). Memory, amnesia, and frontal lobe dysfunction. *Psychobiol.* 15, 21–36.
- Schacter, D.L., and Tulving, E., eds. (1994). *Memory Systems 1994* (Cambridge, MA: MIT Press).
- Schmolck, H., Kensinger, E., Corkin, S., and Squire, L.R. (2002).

- Semantic knowledge in patient H.M., and other patients with bilateral medial and lateral temporal lobe lesions. *Hippocampus* 12, 520–533.
- Shimamura, A.P., and Squire, L.R. (1987). A neuropsychological study of fact memory and source amnesia. *J. Exp. Psychol. Learn. Mem. Cogn.* 13, 464–473.
- Smith, M.E. (1993). Neurophysiological manifestations of recollective experience during recognition memory judgments. *J. Cogn. Neurosci.* 5, 1–13.
- Squire, L.R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* 99, 195–231.
- Squire, L.R., and Shimamura, A.P. (1986). Characterizing amnesic patients for neurobehavioral study. *Behav. Neurosci.* 100, 866–877.
- Squire, L.R., and Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science* 253, 1380–1386.
- Squire, L.R., Amaral, D.G., Zola-Morgan, S., Kritchevsky, M., and Press, G. (1989). Description of brain injury in the amnesic patient N.A. based on magnetic resonance imaging. *Exp. Neurol.* 105, 23–35.
- Stark, C.E.L., and Squire, L.R. (2000). fMRI activity in the hippocampal region during recognition memory. *J. Neurosci.* 20, 7776–7781.
- Stark, C.E.L., and Squire, L.R. (2001). Simple and associative recognition in the hippocampal region. *Learn. Mem.* 8, 190–197.
- Stark, C.E.L., Bayley, P.J., and Squire, L.R. (2002). Recognition memory for single items and for associations is similarly impaired following damage to the hippocampal region. *Learn. Mem.* 9, 234–242.
- Suzuki, W.A., and Amaral, D.G. (1994). Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. *J. Neurosci.* 14, 1856–1877.
- Suzuki, W.A., and Eichenbaum, H. (2000). The neurophysiology of memory. *Ann. N Y Acad. Sci.* 911, 175–191.
- Tulving, E. (1985). Memory and consciousness. *Can. Psychol.* 26, 1–12.
- Tulving, E., and Markowitsch, H.J. (1998). Episodic and declarative memory: role of the hippocampus. *Hippocampus* 8, 198–204.
- Vargha-Khadem, F., Gadian, D.G., and Mishkin, M. (2001). Dissociations in cognitive memory: the syndrome of developmental amnesia. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 1435–1440.
- Vargha-Khadem, F., Gaffan, D., Watkins, K.E., Connelly, A., Van Paesschen, W., and Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science* 277, 376–380.
- Verfaellie, M., and Keane, M.M. (2002). Impaired and preserved memory processes in amnesia. In *The Neuropsychology of Memory*, second edition, L.R. Squire and D. Schacter, eds. (New York: Guilford Press), pp. 35–46.
- Warrington, E.K. (1984). *Recognition Memory Test* (Windsor: FER-Nelson).
- Wood, E.R., Dudchenko, P.A., and Eichenbaum, H. (1999). The global record of memory in hippocampal neuronal activity. *Nature* 397, 561–563.
- Yonelinas, A.P. (2002). The nature of recollection and familiarity: a review of 30 years of research. *J. Mem. Lang.* 46, 441–517.
- Yonelinas, A.P., Kroll, N.E.A., Dobbins, I., Lazzara, M., and Knight, R.T. (1998). Recollection and familiarity deficits in amnesia: convergence of remember-know, process dissociation, and receiver operating characteristic data. *Neuropsychology* 12, 323–339.
- Yonelinas, A.P., Hopfinger, J.B., Buonocore, M.H., Kroll, N.E., and Baynes, K. (2001). Hippocampal, parahippocampal and occipital-temporal contributions to associative and item recognition memory: an fMRI study. *Neuroreport* 12, 359–363.
- Yonelinas, A.P., Kroll, N.E.A., Quamme, J.R., Lazzara, M.M., Sauve, M.J., Widaman, K.F., and Knight, R.T. (2002). Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. *Nat. Neurosci.* 5, 1236–1241.
- Zola, S.M., Squire, L.R., Teng, E., Stefanacci, L., Buffalo, E.A., and Clark, R.E. (2000). Impaired recognition memory in monkeys after damage limited to the hippocampal region. *J. Neurosci.* 20, 451–463.
- Zola-Morgan, S., Squire, L.R., and Amaral, D.G. (1986). Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *J. Neurosci.* 6, 2950–2967.