Memory and the Hippocampus: A Synthesis From Findings With Rats, Monkeys, and Humans

Larry R. Squire
Veterans Affairs Medical Center, San Diego, California
and University of California, San Diego

This article considers the role of the hippocampus in memory function. A central thesis is that work with rats, monkeys, and humans—which has sometimes seemed to proceed independently in 3 separate literatures—is now largely in agreement about the function of the hippocampus and related structures. A biological perspective is presented, which proposes multiple memory systems with different functions and distinct anatomical organizations. The hippocampus (together with anatomically related structures) is essential for a specific kind of memory, here termed *declarative memory* (similar terms include *explicit* and *relational*). Declarative memory is contrasted with a heterogeneous collection of nondeclarative (*implicit*) memory abilities that do not require the hippocampus (skills and habits, simple conditioning, and the phenomenon of priming). The hippocampus is needed temporarily to bind together distributed sites in neocortex that together represent a whole memory.

In recent years a consensus has been developing about the role of the mammalian hippocampal formation in learning and memory. The idea that the hippocampus is important for memory is not in itself new. What is new is that this idea is now supported by direct and compelling evidence for each of the three species that has been important to this work: rats, monkeys, and humans. In addition, there have been major gains in understanding exactly how the hippocampal formation is involved in memory.

Not too many years ago, when the topic of memory and hippocampus was discussed in the context of research on humans and nonhuman primates, the term *hippocampus* could be used only tentatively. Elegant neuropsychological studies of the noted amnesic patient H. M. (Scoville & Milner, 1957) had demonstrated convincingly that memory depends on the integrity of the medial temporal lobe (Milner, 1966). H. M. developed severe amnesia following surgical removal of the medial temporal lobe bilaterally in an attempt to relieve severe epilepsy. Continuing study of H. M. (Corkin, 1984; Milner, 1972) established the fundamental principle that memory could be dissociated from other intellectual functions. However, the medial temporal lobe is a large region that includes the hippocampus, amygdala, and adjacent cortical areas. Although there was reason to believe that the posterior aspect of the lesion was especially critical, that is, the hippocampus and underlying cortex (Scoville & Milner, 1957), precisely what damage within the medial temporal lobe was responsible for H. M.'s amnesia was not known.

In the rat, which has been the most commonly used experimental animal for neurobehavioral studies, it was clear that the hippocampus proper was important for some function, because lesions placed within the hippocampus disrupted behavior in a selective way. However, until recently there has been considerable uncertainty about which tasks are the appropriate ones for detecting behavioral deficits and about how to interpret the deficits.

The purpose of this article is threefold. First, recent evidence is summarized, which brings to a high level of certainty the conclusion that the hippocampus itself is important for memory in humans and nonhuman primates. Indeed, there is now good correspondence among the findings for all the commonly studied mammalian species. Furthermore, the recent evidence suggests that, in addition to the hippocampus proper, certain adjacent and anatomically related cortical structures in the medial temporal lobe (especially entorhinal, perirhinal, and parahippocampal cortex) also participate in memory functions. The components of the medial temporal lobe memory system can now be identified in broad outline.

Second, the idea is developed that the role of the hippocampus (and related cortex) is narrower than once believed. The hippocampus is essential for a specific but important kind of memory—here termed *declarative* memory (other similar terms include *explicit* and *relational* memory). The first suggestion that the hippocampus is involved in only one kind of memory was developed by Hirsh (1974) on the basis of studies of rodents with hippocampal lesions. Subsequently, other hypotheses about hippocampal function were also presented that contained the idea that only a particular kind of memory is dependent on the hippocampus (Gaffan, 1974; O'Keefe & Nadel, 1978; Olton, Becker, & Handelmann, 1979). Eventually, considerable evidence for the idea that only one kind of memory is

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Correspondence concerning this article should be addressed to Larry R. Squire, Veterans Affairs Medical Center, 3350 La Jolla Village Drive, San Diego, California 92161.

affected by hippocampal damage accumulated in demonstrations of entirely intact learning and memory abilities in patients who were otherwise severely amnesic (Cohen, 1984; Squire, 1982). The important implication was that memory is not a single entity. Indeed, in the absence of the hippocampus, several other kinds of learning can still be accomplished, including the learning of skills and habits, simple conditioning, and the phenomenon of priming.

Third, the idea is developed that the role of the hippocampus in memory is time limited. Amnesic patients, including patients with confirmed hippocampal damage, have difficulty recalling the recent past but can recall remote events as well as normal subjects (MacKinnon & Squire, 1989; Squire, Haist, & Shimamura, 1989). Recently, the significance of this observation has been illuminated by a prospective study of retrograde amnesia in the monkey (Zola-Morgan & Squire, 1990c). The findings indicate that the role of the hippocampal formation in memory storage is only temporary. Memory is gradually reorganized as time passes after learning. Memory is initially dependent on the hippocampus formation, but its role diminishes as a more permanent memory is gradually established elsewhere, probably in neocortex.

Identification of the Components of the Medial Temporal Lobe Memory System

Information about which structures and connections are important for memory (and that when damaged produce amnesia) comes from three sources: studies of neurological patients with circumscribed memory impairment, systematic experimental work with an animal model of human amnesia in the monkey, and studies of the effects of selective lesions in rats.

Memory-Impaired Patients

Cognitive studies of memory impairment have provided valuable information about the organization of memory functions (Baddeley, 1982; Cermak, 1982; Milner, 1972; Schacter, 1985; Squire, 1986; Weiskrantz, 1987). The most informative cases have been those where the amnesia occurs against a background of normal intellectual function and intact immediate memory. The hallmark of the disorder is profound forgetfulness for new material (anterograde amnesia) and some loss of previously acquired information (retrograde amnesia). Until recently, comparatively little was known about what neuropathological changes in the medial temporal lobe had occurred in the patients being studied. Several single-case studies attributed memory impairment to hippocampal damage (Cummings, Tomiyasu, Read, & Benson, 1984; DeJong, Itabashi, & Olson, 1968; Duyckaerts et al., 1985; Victor, Angevine, Mancall, & Fisher, 1961), but the assessment of memory functions in these cases was often informal or incomplete. In addition, the damage was often not restricted to the hippocampus but extended into the amygdala, the parahippocampal gyrus, and other structures.

The findings from a carefully studied single case have placed the matter on firmer ground. Patient R. B. became amnesic in 1978 at the age of 52 as the result of an ischemic event that occurred following open-heart surgery (Zola-Morgan, Squire, & Amaral, 1986). *Ischemia* (ISC) refers to a condition during which the blood supply to the brain is insufficient. In R. B.'s case, a clot occurred in the atrium of the heart. R. B. survived for 3 years after the ischemic event, during which time his cognitive functions were repeatedly evaluated and his memory impairment was documented. The only cognitive deficit that was noted was moderately severe memory impairment. Examination of R. B.'s brain after his death in 1983 revealed a lesion in the CA1 region of the hippocampus (Zola-Morgan et al., 1986, Figure 1). The lesion was bilateral and extended the full rostrocaudal extent of the hippocampus. There was some other minor pathology, but the only finding that could reasonably be associated with the amnesia was hippocampal damage. This case thus showed that damage limited to the hippocampus is sufficient to cause easily detectable and clinically significant memory impairment. Recently another case has been reported of memory impairment associated with a bilateral lesion of the hippocampus (Victor & Agamanolis, 1990).

The CA1 region of the hippocampus is especially vulnerable to ischemic damage. Thus, global ischemia in the rat also produces selective neuronal loss in the CA1 region together with memory impairment (Auer, Jensen, & Whishaw, 1989; Davis & Volpe, 1990). Also, as discussed later, bilateral CA1 damage and memory impairment can be found after global ischemia in the monkey (Zola-Morgan & Squire, 1990a; Zola-Morgan et al., in press). The findings from R. B., and the observed effects of global ischemia in the rat and monkey, provide compelling evidence that the hippocampus proper is essential for mammalian memory. The same conclusion is now strongly supported by findings of memory impairment in rats following surgical damage limited to the hippocampus when appropriate tasks are used (Barnes, 1988; Eichenbaum, Mathews, & Cohen, 1989; Olton et al., 1979; Sutherland & Rudy, 1989). The findings with rats are discussed more fully in a later section.

Additional confirmation for the idea that the human hippocampus is important for memory has come from recent improvements in magnetic resonance (MR) imaging, which make it possible to obtain anatomical information in living patients (Figure 1). A high-resolution protocol for imaging human hippocampus was developed that permits visualization of the hippocampal formation in considerable detail (Press, Amaral, & Squire, 1989). Using this protocol, abnormalities in the hippocampus were demonstrated in 4 patients with circumscribed memory impairment (Squire, Amaral, & Press, 1990). Specifically, in the patients, the region of the hippocampus defined as the fimbria, dentate gyrus, hippocampus proper, and subiculum appeared markedly shrunken and atrophic (57% of normal size). In contrast, the area of the temporal lobe excluding the hippocampal region was normal. Thus, the MR technique has been able to provide direct visual evidence of hippocampal damage in patients with a selective memory disorder.

One important finding was that neither patient R. B. nor the 4 other amnesic patients studied with MR imaging were as severely memory impaired as the well-studied surgical patient H. M. (Scoville & Milner, 1957). This observation suggests that the severity of H. M.'s memory impairment resulted from damage to medial temporal lobe structures other than or in addition to the region of the hippocampus itself. Recently it has

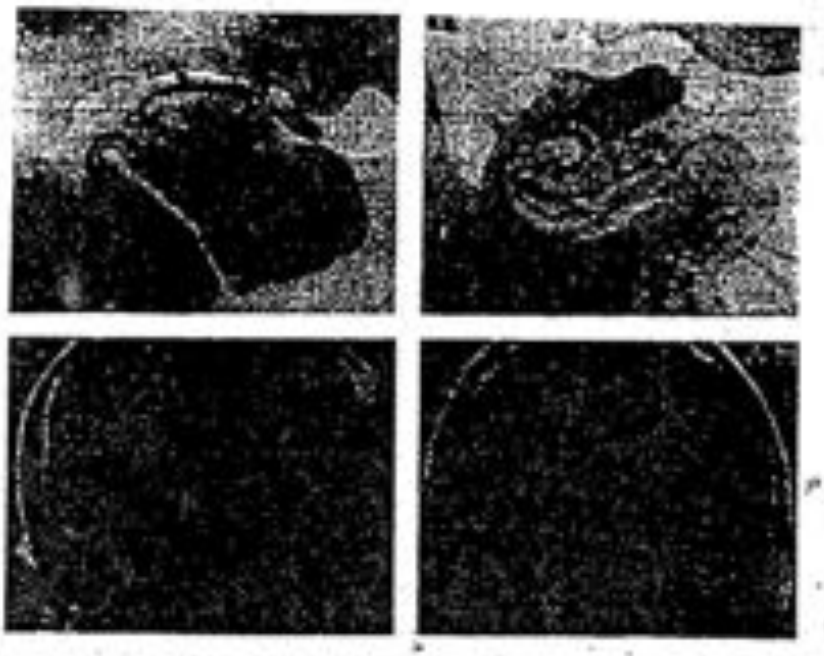

Figure 1. Top left panel: Section through the hippocampus of a normal subject. Top right panel: Section through the hippocampus of amnesic patient R. B. showing damage to the CA1 region. Bottom left panel: Magnetic resonance scan of a normal subject (resolution = .625 mm). Several anatomical features of the hippocampal formation can be distinguished. Bottom right panel: Magnetic resonance scan of amnesic patient W. H. using the same protocol. The hippocampal formation is markedly reduced in size. The calibration bars to the right represent 5 cm in 1-cm increments. (From "Memory: Organization of Brain Systems and Cognition" by L. R. Squire, S. Zola-Morgan, C. B. Cave, F. Haist, B. Musen, and W. Suzuki, 1990, *Cold Spring Harbor Symposium on Quantitative Biology*: 55, p. 1002. Copyright 1990 by Cold Spring Harbor Laboratory. Reprinted by permission.)

become possible to confirm this idea directly using an animal model of human amnesia in the monkey.

Memory Impairment in Nonhuman Primates

In 1978, it was reported that a large medial temporal lobe lesion in monkeys, which was intended to mimic the surgical lesion sustained by patient H. M., caused severe memory impairment (Mishkin, 1978). The lesion included the amygdala, the hippocampus (including the dentate gyrus and subiculum), and surrounding cortical regions (the H-A- lesion, Figure 2). Although more work was needed before the impairment was well understood (Mahut & Moss, 1984; Mishkin, Spiegler, Saunders, & Malamut, 1982; Squire & Zola-Morgan, 1983; for recent reviews, see Squire & Zola-Morgan, 1991; Zola-Morgan & Squire, 1990b), Mishkin's 1978 publication was the first in a new era of research on the anatomy of memory, and in this sense it signaled the successful development of an animal model of human amnesia in the nonhuman primate (Table 1). The H-A- lesion was used frequently in early work on the animal model of human amnesia. However, the effects of more limited lesions involving the hippocampal formation were also of interest, primarily because of the early suggestion (Scoville & Milner, 1957) that damage to the hippocampal region might be especially important in understanding patient H. M.'s amnesia. A lesion of the hippocampal formation is ordinarily produced by a direct surgical approach through the ventral surface of the brain that damages the hippocampus proper, the dentate gyrus, the subicular complex, together with the underlying cortex that is necessarily removed in order to reach the hippocampus, that is, the posterior entorhinal cortex and much of the parahippocampal gyrus. This more restricted lesion has been termed *H*+, where *H* refers to the hippocampus and + to the underlying cortex (see Figure 2).

Monkeys with the H+ lesion are impaired on a variety of memory tasks (Mahut, Moss, & Zola-Morgan, 1981; Moss, Mahut, & Zola-Morgan, 1981; Zola-Morgan & Squire, 1986; Zola-Morgan, Squire, & Amaral, 1989a) that are also failed by human amnesic patients (Squire, Zola-Morgan, & Chen, 1988; see Table 2). The tasks used to demonstrate memory impairment include retention of easy object discriminations, eight-pair concurrent discrimination learning, and delayed response with delays tested up to 30 s (Zola-Morgan & Squire, 1990b). It is useful to emphasize that simple object-discrimination tasks and concurrent object-discrimination tasks, which require several object pairs to be learned together, are among the tasks sensitive to H+ lesions. Simple object-discrimination tasks are ones that present to the animal two easily distinguishable objects. A choice of the correct object is rewarded, and the sequence is repeated until animals choose the rewarded object consistently (10 to 20 trials for normal monkeys). Concurrent discrimination tasks are ones in which different pairs of objects are pre-

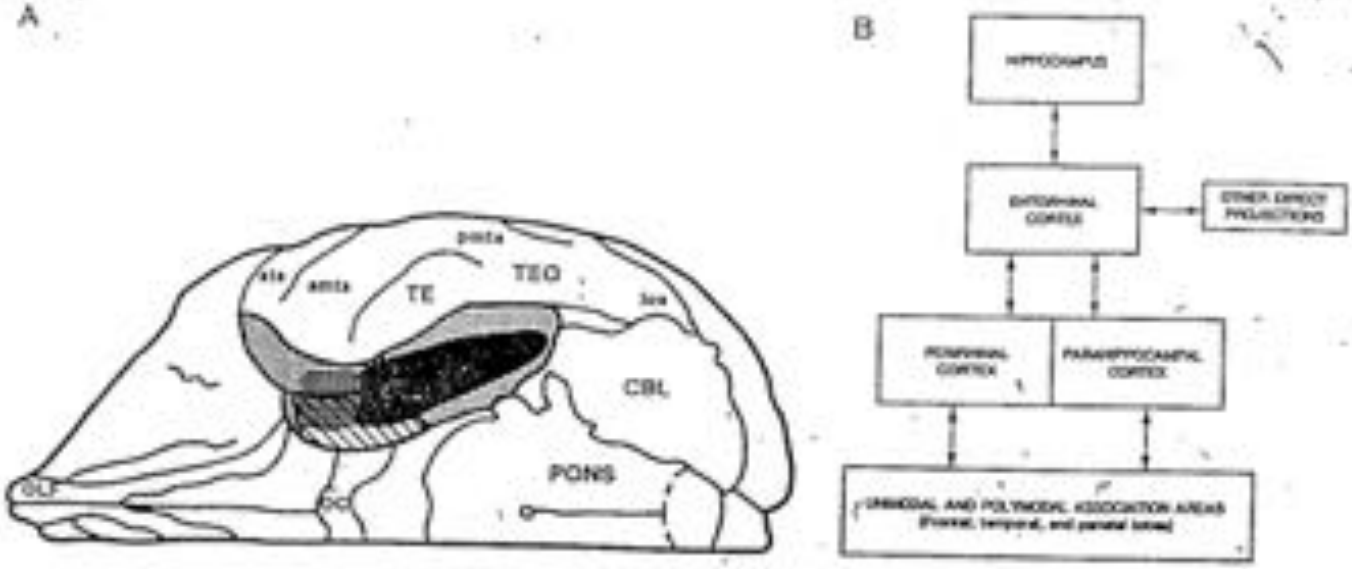

Figure 2. Panel A: A ventral view of the left hemisphere of a monkey brain showing the components of the large H'A" lesion that first established an animal model of human amnesia. *H* = hippocampus, *A* = amygdala; and + refers to the adjacent cortex underlying each structure [perlamygdaloid cortex, perirhinal cortex, entorhinal cortex, and parahippocampal cortex]. The view shows the amygdala [square-shaped black-and-white plaid], the hippocampus [black], and the underlying cortical regions typically included in surgical ablations of these structures. Large dots = perirhinal cortex; horizontal lines = perlamygdaloid cortex; diagonal lines = entorhinal cortex; fine dots = parahippocampal cortex. Panel B: A schematic view of the structures of the medial temporal lobe important for declarative memory. The entorhinal cortex is the major source of inputs to the hippocampus. Approximately two thirds of the input to entorhinal cortex originate in the perirhinal and parahippocampal cortices. The entorhinal cortex also receives other direct projections from orbital frontal cortex, cingulate cortex, insular cortex, and superior temporal gyrus. As indicated, all of these projections are reciprocal. In the figure, the area designated hippocampus includes dentate gyrus, the cell field of the hippocampus proper, and the subicular complex. sts = superior temporal sulcus; amts = anterior middle temporal sulcus; pmts = posterior middle temporal sulcus; ios = inferior occipital sulcus; CBL = cerebellum; OLF = olfactory bulb; OC = optic chiasm. (Panel A: From "Neuropsychological Investigations of Memory and Amnesia: Findings From Humans and Nonhuman Primates," p. 442, by S. Zola-Morgan and L. R. Squire, 1990, in A. Diamond, *The Development and Neural Bases of Higher Cognitive Functions*, New York: New York Academy of Sciences. Copyright 1990 by the New York Academy of Sciences. Reprinted by permission. Panel B: From "The Medial Temporal Lobe Memory System" by L. R. Squire and S. Zola-Morgan, 1991, *Science 253*, p. 1380. Copyright 1991 by the American Association for the Advancement of Science. Reprinted by permission.)

sented successively (e.g., eight pairs of objects, five times each during 40 daily trials). Training continues until animals choose consistently the rewarded object of each pair (several hundred trials for normal monkeys). In contrast to these tasks, the learning of pattern discrimination tasks and learning of the 24-hr concurrent discrimination task (Malamut, Saunders, & Mishkin, 1984) are not affected by even larger removals within the medial temporal lobe (for discussions of this difference, see Mishkin, Malamut, & Bachevalier, 1984; Squire & Zola-Morgan, 1983). The point is that monkeys with H" lesions can succeed at certain skill-based or habit-based tasks (Mishkin, Malamut, & Bachevalier, 1984; Zola-Morgan & Squire, 1984). The significance of this finding is developed later in the article.

The most widely used task sensitive to H" lesions has been delayed nonmatching to sample. This task requires an animal to remember a single visual object across a delay (up to 10 min) and then to demonstrate recognition of the object at the end of the delay. Recognition is tested by presenting the animal with a two-choice test (the original object and a new one) and rewarding a choice of the new object. New pairs of objects are used on each succeeding trial.

Monkeys with H" lesions are impaired on delayed nonmatching to sample (Figure 3), as well as on the other tasks mentioned earlier. Performance is good when the delay between presentation of the sample object and the choice is short and it becomes poorer as the delay increases (Overman, Ormsby, & Mishkin, 1990). The scores of both normal and operated animals are lower when monkeys are trained and tested postoperatively (Mahut, Zola-Morgan, & Moss, 1982; Zola-Morgan & Squire, 1986; Zola-Morgan, Squire, & Amaral, 1989a) than when monkeys are first trained preoperatively and then tested postoperatively (Mishkin, 1978). Also, the magnitude of the deficit, that is, the difference between the scores obtained by normal and operated animals, appears numerically larger when training and testing are done postoperatively as compared with preoperatively. However, signal-detection analysis suggests that the defi-

Table 1
Characteristics of Human Amnesia That Have Been Produced in Monkeys With Large Bilateral Medial Temporal Lobe Removals

Characteristic	Reference
Selective loss of one kind of memory (declarative)	Malamut, Saunders, & Mishkin, 1984; Zola-Morgan & Squire, 1984, 1985
Sparing of skill-based memory	Malamut et al., 1984; Zola-Morgan & Squire, 1984
Severity of memory impairment dependent on locus and extent of damage	Mishkin, 1978; Zola-Morgan & Squire, 1985, 1986
Immediate memory is spared	Mishkin, 1978; Overman, Ormsby, & Mishkin, 1990; Zola-Morgan & Squire, 1985
Memory is impaired when the number of stimuli exceeds immediate memory capacity	Zola-Morgan & Squire, 1985
Distraction exacerbates the memory impairment	Zola-Morgan & Squire, 1985
Memory impairment is modality general	Murray & Mishkin, 1984
Memory impairment can be enduring	Zola-Morgan & Squire, 1985

Note. References are to representative studies and are not exhaustive. From "Neuropsychological Investigations of Memory and Amnesia: Findings From Humans and Nonhuman Primates" (p. 438) by S. Zola-Morgan and L. R. Squire, 1990, in A. Diamond, *The Development and Neural Bases of Higher Cognitive Functions*, New York: New York Academy of Sciences. Copyright 1990 by the New York Academy of Sciences. Adapted by permission.

cits in these two conditions are equivalent (Ringo, 1988). Preoperative training improves postoperative performance of both normal and operated animals and brings their scores closer together as the performance ceiling is approached. The benefit of preoperative training for postoperative performance is probably due to postoperative savings of some preoperatively acquired information about the rules of the task as well as postoperative retention of certain skills that could assist in the task of remembering a new sample object across a delay (e.g., attention and immobility). Some of this information probably survives medial temporal lobe surgery, as has been shown directly for motor skills (Salmon, Zola-Morgan, & Squire, 1987), and it facilitates the relearning of the task and the ability to remember new objects across a delay.

Useful information about which medial temporal lobe structures are important for memory functions can be obtained by comparing the severity of memory impairment in different groups of animals. For example, in studies of monkeys with ischemic damage to the hippocampus, one can ask whether a detectable memory impairment is produced in the monkey and whether the memory impairment, if detectable, is less severe or more severe than the impairment associated with the H lesion (Rempel, Clower, Amaral, Zola-Morgan, & Squire, 1991; Zola-Morgan et al., in press). Ischemia was produced by 15-min

Table 2
Performance of Amnesic Patients and Monkeys With H A* Lesions on the Same Tasks*

Test	Amnesic patients		Monkeys with H*A* lesions	
	+/−	Reference	+/−	Reference
Delayed nonmatching to sample	+	Squire, Zola-Morgan, & Chen, 1988; Oscar-Berman & Bonner, 1985	+	Mishkin, 1978; Zola-Morgan & Squire, 1985
Retention of object discrimination	+	Squire, Zola-Morgan, & Chen, 1988	+	Zola-Morgan & Squire, 1985
8-pair concurrent discrimination	+	Squire et al., 1988; Oscar-Berman & Bonner, 1985	+	Zola-Morgan & Squire, 1985
Object reward association	+	Squire et al., 1988	+	Phillips & Mishkin, 1984
24-hr concurrent discrimination	+	Squire et al., 1988	−	Malamut, Saunders, & Mishkin, 1984
Motor skill learning	−	Pursuit rotor task; Brooks & Baddeley, 1976	−	Lifesaver task; Zola-Morgan & Squire, 1984
Pattern discrimination	+	Predicted outcome; not yet tested	−	Zola-Morgan & Squire, 1984

Note. References are to representative studies and are not exhaustive. Plus sign indicates impairment; minus sign indicates no impairment. Monkeys may approach the 24-hr concurrent-discrimination task and the pattern-discrimination task differently than humans approach these two tasks. Humans try simply to memorize which stimulus is correct and which is incorrect (i.e., using declarative memory). Monkeys gradually learn incrementally, perhaps by gradually strengthening associations or by "tuning in" relevant dimensions of the stimuli (for fuller discussion, see Zola-Morgan & Squire, 1984). From "Neuropsychological Investigations of Memory and Amnesia: Findings From Humans and Nonhuman Primates" (p. 446) by S. Zola-Morgan and L. R. Squire, 1990, in A. Diamond, *The Development and Neural Bases of Higher Cognitive Functions*, New York: New York Academy of Sciences. Copyright 1990 by the New York Academy of Sciences. Adapted by permission.

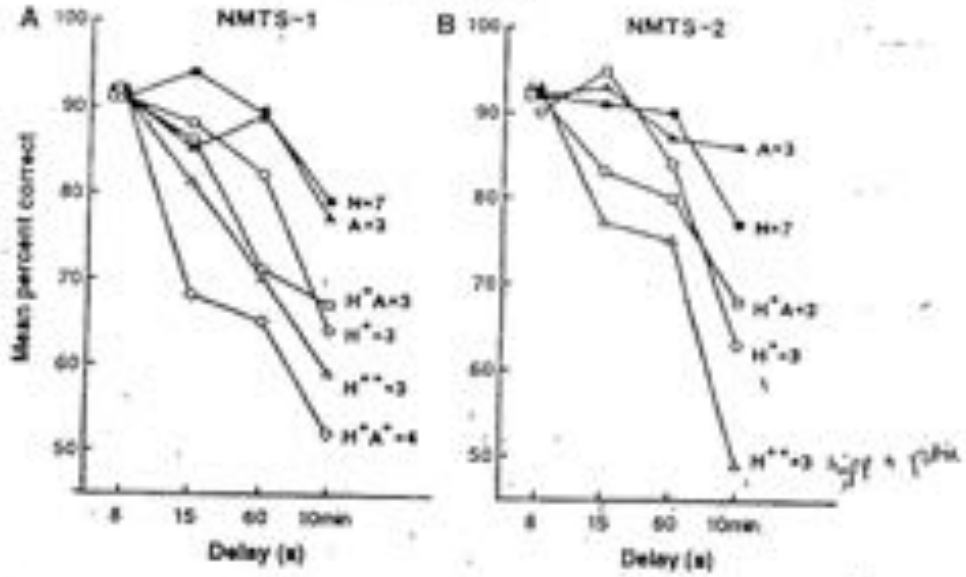

Figure 1. Performance on the delayed-nonmatching-to-sample (NMTS) task by normal monkeys (N), monkeys with lesions of the amygdala (A), monkeys with damage to the hippocampal formation (H), monkeys with conjoint lesions of the hippocampal formation and the amygdala (HA), monkeys with large medial temporal lobe resections (HA*), and monkeys with lesions of the hippocampal formation and the perirhinal cortex adjacent to the amygdala (H**). The numbers in the figure show the number of animals in each group. Performance was tested approximately 1 month after surgery (NMTS-1) and then again 1 to 2 years after surgery (NMTS-2). The performance curve for the H** group in the left panel may underestimate the memory deficit, because one animal in this group required a remedial procedure in which the sample object was always presented twice instead of once. The HA* group was tested only once. (From "The Medial Temporal Lobe Memory System" by L. R. Squire and S. Zola-Morgan, 1991, *Science, 253*, p. 1382. Copyright 1991 by the American Association for the Advancement of Science. Reprinted by permission.)

bilateral carotid occlusion together with pharmacologically induced hypotension. Monkeys prepared in this way had cell loss restricted mainly to the CA1 field of the hippocampus and to somatostatin-containing cells in the dentate gyrus. Only minor, occasional histological damage could be detected in other brain regions. Monkeys with this lesion (ISC) also had impaired memory although the impairment was less severe overall than the impairment associated with surgical lesions of the hippocampal formation (the H* lesion). Specifically, on the delayed nonmatching to sample task monkeys with ischemic lesions were impaired to about the same degree as monkeys with H* lesions. However, on two other tasks (object discrimination and eight-pair concurrent discrimination), monkeys in the ISC group performed better ($p = .06$) than monkeys with H* lesions.

It has also been possible to compare monkeys with ISC lesions to monkeys with selective lesions of the hippocampus, which were produced using stereotaxic coordinates established by MR imaging (the H lesion). The H lesion damaged the hippocampus, dentate gyrus, and subiculum, but spared the underlying cortex (Alvarez-Royo, Clower, Zola-Morgan, & Squire, 1991; Clower, Alvarez-Royo, Zola-Morgan, & Squire, 1991). Monkeys with the H lesion performed similarly to monkeys with ISC lesions across all the tasks and significantly better than H* monkeys on two of the tasks. The findings for ISC lesions, taken together with the findings for H and H* lesions, show that even incomplete damage to the hippocampus is sufficient to produce detectable memory impairment in monkeys, just as it can in humans (patient R. B).

It has been difficult to rule out entirely the possibility that some additional ischemic damage affecting memory functions did occur in patient R. B. and that this damage was not detected in histological analysis. The results with ischemic monkeys are able to illuminate this issue to some extent. Specifically, if significant additional damage had occurred in the ISC monkeys in areas important for memory function, one would expect the memory impairment to have approximated more closely or even to have exceeded the memory impairment associated with surgical lesions of the hippocampal formation. However, the ISC lesion produced less severe memory impairment overall than the H* surgical lesion and about the same level of impairment as H surgical lesions. Accordingly, it is implausible that the ischemic animals (and by analogy the ischemic patient R. B) had widespread pathological change affecting memory that was not subsequently detected by histological examination. The pathology in the ischemic animals must involve less tissue in structures related to memory function than is involved in the H* lesion itself.

Although the H* lesion produces a considerable degree of memory impairment, the level of the deficit is unmistakably greater after a larger bilateral medial temporal lobe removal (the HA* lesion; Mishkin, 1978; Zola-Morgan & Squire, 1985;

Zola-Morgan et al., 1989a). The finding that H*A* lesions produce more severe memory impairment than H* lesions (Figure 3) implies that some of the damage produced by the H*A* lesion, which is not included in the H* lesion, are important for memory functions. Herein lies the explanation for why H. M. is more amnesic than other amnesic study patients, including R. B. H. M. sustained an H*A* lesion, but R. B. sustained a lesion involving only a portion of the hippocampus.

Considerable effort has been directed toward identifying which structures are damaged in the H*A* lesion but not in the H* lesion. The early evidence on this point seemed to point to the amygdala (Milhkin, 1978; Murray & Mishkin, 1985; Saunders, Murray, & Mishkin, 1984). However, all these early studies were based on surgical groups in which the amygdala was removed together with underlying cortex. At the same time, the cytoarchitectonics and connectivity of the underlying cortex were incompletely understood, and there was little basis for supposing that it should contribute to memory function. The underlying cortex was only incidentally involved in these surgical procedures, not a target of study.

An early hint that the underlying cortex might play a role in memory came from behavioral studies of monkeys in which anteroventral temporal cortex was reversibly cooled (Horel & Pytko, 1982). When surgical lesions of this area were produced, the most affected animal had a lesion that involved perirhinal cortex (Horel, Pytko-Joiner, Voytko, & Salsbury, 1987). The possibility of studying this cortical region improved considerably when the territory of the perirhinal cortex was defined by modern neuroanatomical methods, and its connectivity with the hippocampal formation was established (Insausti, Amaral, & Cowan, 1987). The entorhinal cortex was already known to be the source of the major afferent projection to the hippocampus and dentate gyrus. The important newer finding was that the adjacent perirhinal and parahippocampal gyrus provide nearly two thirds of the cortical input to the entorhinal cortex. Perirhinal and parahippocampal cortex are therefore essential for the normal exchange of information between the neocortex and the hippocampal formation.

With these anatomical facts in mind, we reexamined a group of H*A* monkeys (Zola-Morgan, Squire, & Mishkin, 1982) that had been prepared with the standard surgical approach to the amygdala. Substantial damage to perirhinal cortex had occurred in all the animals (see Zola-Morgan, Squire, Amaral, & Suzuki, 1989). On the basis of this observation, it seems plausible that damage to perirhinal cortex adjacent to the amygdala would also have occurred during the similar surgical approach used to make more limited lesions directed at the amygdala itself or the amygdalofugal pathway (Bachevalier, Saunders, & Mishkin, 1985; Mishkin, 1978). In short, it appears that the lesions in the earlier studies that were intended to test the role of the amygdala had damaged cortex in addition to the amygdala that on anatomical grounds might be expected to have a role in memory function.

It thus became important to determine experimentally the separate contributions to memory impairment of amygdala damage and damage to underlying cortex. To evaluate the effect of amygdala damage itself on memory, we developed a surgical procedure involving bilateral stereotaxic lesions, which damaged virtually all the components of the amygdaloid complex but spared adjacent cortex (the A lesion). Monkeys with the A lesion performed normally on four memory tasks (delayed nonmatching to sample, retention of object discriminations, concurrent discrimination, and delayed response (Zola-Morgan, Squire, & Amaral, 1989b). In contrast, monkeys with H* or H*A* lesions were impaired on all four tasks. We also evaluated monkeys who had bilateral lesions of the hippocampal formation (H*) made conjointly with circumscribed lesions of the amygdaloid complex (the H*A lesion). The H*A monkeys were also impaired on the four memory tasks, but their impairment was no greater than after H* lesions. Thus, amygdala damage alone did not impair memory; nor did it exacerbate the memory impairment associated with damage to the hippocampal formation (Figure 3).

These findings suggested that more severe memory impairment observed after H*A* lesions might be attributable to damage to the cortical regions that surround the amygdala. This possibility was tested directly in two different ways. First, monkeys were prepared with H* lesions that were brought forward to include the anterior entorhinal cortex and much of the perirhinal cortex (the H** lesion). The intention in this group was to reproduce as much of the H*A* lesion as possible but to leave the amygdala intact. On delayed nonmatching to sample, the impairment associated with H** lesions was nearly as severe as that following H*A* lesions (Figure 3) and significantly more severe than the impairment following either H* or H*A lesions (Squire & Zola-Morgan, 1991). Thus, lesions of the cortex surrounding the amygdala, but not lesions of the amygdala itself, exacerbated memory impairment in monkeys following lesions of the hippocampal formation. The H** monkeys were also as impaired as H*A* monkeys on a second task: object-discrimination learning.

The second test of the idea that the cortical regions surrounding the amygdala are important for memory was motivated by current understanding of the anatomical connections of the hippocampus and adjacent cortex (Figure 2). In particular, as described earlier, perirhinal and parahippocampal cortex are major routes by which information is exchanged between the neocortex and the hippocampal formation. Accordingly monkeys were prepared with bilateral lesions limited to the perirhinal cortex and parahippocampal gyrus (PRPH) that spared the hippocampus, the amygdala, and the entorhinal cortex (Zola-Morgan, Squire, Amaral, & Suzuki, 1989). The white matter underlying perirhinal cortex was also transected in an attempt to remove other cortical input to entorhinal cortex. These monkeys were severely impaired on the three memory tasks they were given (delayed nonmatching to sample, object discrimination, and concurrent discrimination). In general, the impairment following PRPH lesions was similar to that observed following H*A* lesions and H** lesions. Histological analysis showed that, as intended, damage had occurred not only to the perirhinal and parahippocampal cortex but also to projections to the entorhinal cortex from orbitofrontal cortex, superior temporal gyrus, insula, and cingulate gyrus.

It is unlikely that the severe memory deficit after either PRPH lesions or H** lesions resulted from indirect effects of these lesions on the function of the amygdala. This possibility merits consideration because perirhinal cortex does originate direct projections to the amygdala (Amaral, 1987; Van Hoesen,

1981). However, there are two difficulties with the idea that damage to these projections contributed to the memory impairment. First, removal of the amygdala itself had no effect on memory. Second, quantitative studies of emotional behavior have been carried out with the same operated groups that were given memory tests. The finding was that either partial or complete damage to the amygdala caused readily detectable changes in emotional behavior as evidenced by an abnormal tendency to approach or touch stimulus objects (Zola-Morgan, Squire, Alvarez-Royo, & Clower, 1991). Yet, monkeys with PRPH lesions exhibited normal emotional behavior. Indeed a double dissociation was found. Among six operated groups, the groups of monkeys with amygdala damage exhibited abnormal emotional behavior. Unless there was also hippocampal damage, memory was unaffected. Conversely, all operated groups with damage to the hippocampus or its associated cortex exhibited memory impairment. However, unless the amygdala was also damaged, emotional behavior was normal.

The findings from PRPH lesions and H^{++} lesions, taken together with the finding of intact memory after circumscribed amygdala damage, strongly suggest that the severe memory impairment associated with large medial temporal lobe lesions (H^{+A} lesions) results from damage to the hippocampal formation and adjacent anatomically related cortex, not from conjoint damage to the hippocampus and amygdala. One important implication of these studies with monkeys is that the cortex adjacent to the hippocampus is not simply a conduit for funneling information from neocortex to the hippocampus. This conclusion follows from the finding that the PRPH lesion and the H^{++} lesion produced a more severe memory impairment than the H^{+} lesion and also from the finding that the H^{+} lesion produced a more severe impairment than the H lesion.

Thus, it appears that information from neocortex need not reach the hippocampus itself for some memory storage to occur (Figure 4). The cortical structures adjacent to the hippocampus (entorhinal, perirhinal, and parahippocampal cortex) appear to participate with the hippocampus in a common memory function. This idea explains why memory impairment can be increased by lesions in structures adjacent to the hippocampus. These cortical structures in the medial temporal lobe are sites of convergent projections from widespread unimodal and polymodal association areas in neocortex, and these connections are reciprocal (Amaral, 1987; Van Hoesen, 1982). The entorhinal cortex itself (which projects directly to hippocampus) receives direct cortical input from a limited number of cortical areas. The perirhinal and parahippocampal cortices (and the other cortical regions that project to entorhinal cortex) receive information from and send information to a much broader extent of neocortex. Thus, the system as a whole is likely to be privy to much of the processing that occurs in neocortex.

In summary, the findings from work with monkeys emphasize the importance for memory functions of the hippocampal formation and the surrounding cortex of the medial temporal lobe. Other recent work in monkeys and humans is consistent with this proposal (Friedman & Goldman-Rakic, 1988; George, Horel, Cirillo, 1989; Squire, Ojemann, Miezin, Petersen, Videen, & Raichle, in press; Van Hoesen & Damasio, 1987). It seems likely that the medial temporal lobe memory system influences memory primarily through its reciprocal projections with widespread areas of neocortex. In separate studies, damage to the major efferent system of the hippocampal formation, the fornix, and damage to the major diencephalic target of the fornix, the mammillary nuclei, had only mild effects on memory using the same tasks (Aggleton & Mishkin, 1985; Bachevalier et al., 1985; Zola-Morgan et al., 1989a). These latter findings do not describe the severity of memory impairment in any absolute sense, but they make the important point that the impairment after fornix section or mammillary nuclei lesions is less severe than after damage to the hippocampal formation.

Another region of the brain that when damaged produces amnesia is the medial thalamus. Medial thalamic lesions in the monkey produce severe memory impairment (Aggleton & Mishkin, 1983). It is not yet entirely clear which thalamic nuclei must be damaged to cause amnesia (for a review, see Zola-Morgan & Squire, in press). The areas most often linked to memory functions are the medial dorsal nucleus, the anterior nucleus, the internal medullary lamina, and the mammillothalamic

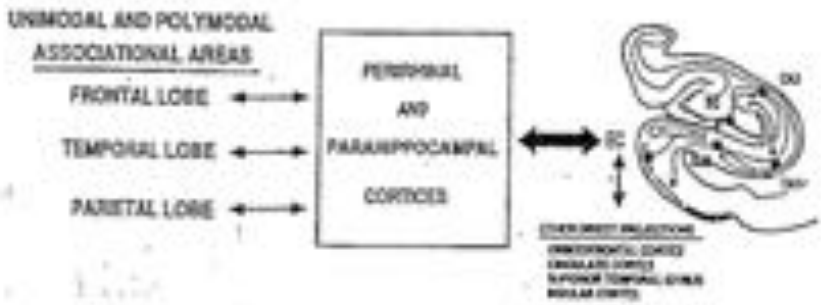

Figure 4. Schematic representation of the connectivity of the perirhinal and the parahippocampal cortices in the monkey brain. The width of the arrows corresponds to the relative proportion of cortical inputs arising from the areas indicated. EC = entorhinal cortex; DG = dentate gyrus; SUB = subicular complex; CA3 and CA1 are fields of the hippocampus proper. (From "Memory: Organization of Brain Systems and Cognition" by L. R. Squire, S. Zola-Morgan, C. B. Cave, F. Haist, G. Musen, and W. Suzuki, 1990, *Cold Spring Harbor Symposium on Quantitative Biology, 55*, p. 1019. Copyright 1990 by Cold Spring Harbor Laboratory. Reprinted by permission.)

tract (Aggleton & Mishkin, 1983; Graff-Radford, Tranel, Van Hoesen, & Brandt, 1990; Squire, Amaral, Zola-Morgan, Kritchevsky, & Press, 1989; Victor, Adams, & Collins, 1989; von Cramon, Hebel, & Schuri, 1985). Most of these thalamic regions have anatomical connections to either the hippocampal formation or the perirhinal cortex. It is also unclear to what extent diencephalic and medial temporal lobe pathology in humans and monkeys might produce different patterns of memory impairment (for two points of view, see Parkin, 1984; Victor et al., 1989). Although one would expect that these brain regions make different contributions to normal memory, each region may belong to a tightly linked functional system such that damage to any component causes rather similar kinds of impairment.

Memory Impairment in Rats

During the past several years, many points of contact have developed between work with rats and work with humans and nonhuman primates. In the rat, hippocampal lesions or lesions of related structures (fornix or entorhinal cortex) impair performance on a wide variety of memory tasks. These include spatial memory tasks, odor-discrimination learning, timing tasks, and discrimination tasks that require learning relationships between stimuli. One major focus of this work has been to characterize the kind of learning and memory that is impaired (see next section). Another focus has been to compare the effects of hippocampal lesions with the effects of lesions in adjacent structures.

Studies directed at this second objective have obtained two important findings. The first pertains to the roles of the hippocampus and the amygdala in memory. The second pertains to the separate contributions of the structures and connections within the hippocampal formation. First, at least seven examples can be identified where hippocampal lesions or lesions of anatomically related structures produce an effect on memory, but amygdala lesions produce no impairment (Table 3). In addition, three studies have found that adding an amygdala lesion to a lesion of the hippocampal system did not increase the deficit beyond what was observed following the hippocampal lesion alone (Aggleton, Hunt, & Rawlins, 1986, Experiment 2; Eichenbaum, Fagan, & Cohen, 1986; Sutherland & McDonald, 1990). One important feature of the studies with rats is that amygdala lesions were typically produced stereotaxically. This procedure makes it possible to produce amygdala lesions without damaging cortical areas surrounding the amygdala.

An apparent exception to this pattern of findings is a report that conjoint lesions of amygdala and hippocampus impaired performance on a task of object recognition, whereas separate lesions of hippocampus or amygdala had no effect, even when animals had to retain information up to delays of 60 s (Aggleton, Blindt, & Rawlins, 1989). This task was a modified version of the visual delayed nonmatching-to-sample task used with monkeys. Rats were rewarded for choosing the arm of a Y maze that differed visually from the starting arm. Multiple, removable arms were used so that on each trial rats saw one arm identical to the starting arm and a second arm that differed from the starting arm along several dimensions. Although one might expect from studies of monkeys that performance on such a task should be measurably impaired by hippocampal lesions alone (Malutt et al., 1982; Mishkin, 1978; Zola-Morgan et al., 1989a), rats with hippocampal lesions performed this task normally. Because hippocampal lesions alone did not disrupt performance on this task, it is difficult to interpret the impairment that occurred with larger lesions. One possibility, which has scarcely been explored, is that rats might approach some variants of the delayed nonmatching-to-sample task with a different strategy than nonhuman primates. For example, Sutherland and Rudy (1989) pointed out that this task could in principle be solved by two fundamentally different strategies (also see the note to Table 2 for the importance of strategy differences in how monkeys and humans accomplish pattern-discrimination learning).

In any case, there is no evidence that amygdala lesions in rats impair performance on tasks that are also impaired by hippocampal lesions. The findings in rats are therefore in agreement with the findings from monkeys, namely that the hippocampus and related structures participate in a particular kind of memory function and that the amygdala is not part of this functional system. Indeed, work in both monkeys and rats suggests that the amygdala is important for other functions, including the acquisition of conditioned fear and the establishment of affective significance for neutral stimuli, as expressed, for example, by the development of conditioned responses that are directed toward conditioned stimuli (Davis, 1986; Gaffan & Harrison,

Table 3
Effects of Lesions of the Hippocampal System or the Amygdala on Memory Tasks in the Rat

Task	Hippocampus	Amygdala	Reference
Water maze	+	–	Sutherland & McDonald, 1990
Odor discrimination	+	–	Eichenbaum, Fagan, & Cohen, 1986*
Timing of events	+	–	Olton, Meck, & Church, 1987*
Learning cue relationships	+	–	Sutherland, McDonald, Hill, & Rudy 1989
Spatial alternation	+	–	Aggleton, Hunt, & Rawlins, 1986; Aggleton, Blindt, & Rawlins, 1989
Nonspatial alternation	+	–	Raffaele & Olton, 1988*
Radial maze	+	–	Becker, Walker, & Olton, 1980*

Note. Plus sign indicates impairment; minus sign indicates no impairment.
* These lesions damaged the fornix rather than the hippocampus itself.

1987; Gallagher, Graham, & Holland, 1990; Kesner, in press; LeDoux, 1987; Nachman & Ashe, 1974; Sutherland & McDonald, 1990). It is possible, too, that the amygdala has a more general role in forming associations between stimuli, for example, in making associations across modalities (Murray & Mishkin, 1985). However, when these ideas are based on amygdala lesions prepared by a direct surgical approach, the contribution of underlying cortical regions included in the amygdala lesions needs to be evaluated.

The second important and anatomically relevant finding to emerge from work with rats is that the deficit associated with restricted hippocampal lesions can be increased by additional damage to anatomically related structures and fiber tracts such as the subiculum or the alveus (Jarrard, 1986; Morris, Schenk, Tweedie, & Jarrard, 1990). These findings are in agreement with the findings from monkeys that different levels of impairment can be produced depending on the extent of damage within the medial temporal lobe (e.g., the H* lesion vs. the H** lesion). As described earlier, the same is also true in humans (e.g., patient R. B. vs. H. M.).

Multiple Memory Systems

Progress in identifying the structures and connections that make up the medial temporal lobe memory system has been paralleled by gains in understanding how this system participates in memory functions. An important step in this achievement was the insight that the hippocampal formation is important for only a particular kind of memory. The implication was that memory is not a single entity but consists of multiple processes or systems. Converging evidence about the selective role of the hippocampal formation in memory is now available from rats, monkeys, and humans.

It took time for the idea of multiple memory systems to become firmly established. In 1962, the severely impaired amnesic patient H. M. was reported to be capable of day-to-day improvement in a hand–eye coordination skill, despite having no memory for the practice sessions (Milner, 1962). Nevertheless, subsequent discussions of memory in general and amnesia in particular tended to set aside motor skill learning and to focus on the unitary nature of the rest of memory. Amnesia was considered to impair memory globally, with the recognition that an exception should be made for motor skills.

Findings of unexpectedly good learning by amnesic patients on tasks not requiring motor skills were also reported many years ago. Specifically, patients performed well when the retention test provided partial information (e.g., fragments) about previously presented pictures or words (Milner, Corkin, & Teuber, 1968; Warrington & Weiskrantz, 1968, 1970, 1974, 1978). However, there were two reasons why these reports, and others that followed, did not lead to the idea of multiple memory systems. First, although the performance of amnesic patients was sometimes good, or at least better than might have been expected, it was often below normal levels. Accordingly, the data were open to a proportionality interpretation, namely that some tasks are simply easier than other tasks or provide more sensitive measures of memory. It could therefore be argued that certain task conditions simply improve performance in normal subjects and amnesic patients alike. Second, even when amnesic patients appeared to perform normally, the data could be interpreted as evidence that amnesia is a retrieval deficit that can be reversed when the appropriate tasks are selected (Warrington & Weiskrantz, 1970; Weiskrantz, 1978).

Subsequently, it was discovered that motor skills are just one example of a broader category of skill learning that is intact in amnesic patients (Cohen, 1984; Cohen & Squire, 1980; Squire, 1982). At the same time, the success of partial information at the time of retrieval in eliciting recall in amnesic patients came to be better understood (e.g., word stems like inc... or mot.... as cues for recently studied words). It turned out that only one kind of instruction yields normal performance (complete the stem to form the first word that comes to mind; Graf, Squire, & Mandler, 1984). With conventional memory instructions (use the stem as a cue to recall a recently presented word), normal subjects maintain their advantage over amnesic patients (Graf et al., 1984; Squire, Wetzel, & Slater, 1978). Intact performance by amnesic patients on such tasks, when indirect instructions are used, is now understood as an example of word priming, and a large body of work has accumulated with both normal subjects and amnesic patients in support of the idea that priming reflects a different kind of memory than the kind that is tapped in conventional memory experiments (Shimamura, 1986; Tulving & Schacter, 1990).

The emergence of the idea that memory consists of different systems (Cohen, 1984; Moscovitch, 1982; Schacter, 1987; Squire, 1982; Tulving, 1985; Weiskrantz, 1987; Wickelgren, 1979) was influenced greatly by work with amnesic patients. In addition, experimental work with normal subjects was influential (for reviews, see Hintzman, 1990; Polster, Nadel, & Schacter, 1991; Richardson-Klavehn, & Bjork, 1988). Distinctions between kinds of memory can be found in earlier writings that reflect the traditions of developmental psychology (Bruner, 1969; memory with record and memory without record), psychology (Bergson, 1911; memory and habit), philosophy (Ryle, 1949; knowing how and knowing that), and artificial intelligence (Winograd, 1975; Winston, 1977; declarative and procedural).

The tradition of work with amnesic patients explains why the idea of multiple memory systems led naturally to a consideration of what kind of memory depends on the integrity of the brain structures, including hippocampus, that are damaged in amnesia. In addition, the idea that the hippocampus might be involved in only one kind of memory appeared independently in the animal literature, on the basis of the selective effects of limbic lesions (Gaffan, 1974; Hirsh, 1974; O'Keefe & Nadel, 1978; Olton et al., 1979). The sections that follow suggest that the findings from humans and experimental animals, including rats and monkeys, are now in substantial agreement about the kind of memory that depends specifically on the hippocampus and related structures.

This kind of memory has been termed declarative (Cohen & Squire, 1980) in the sense that one can bring to mind or declare the content of this kind of memory (for its earlier use in psychology see Anderson, 1976). The term *declarative* was derived from work with human subjects and has been difficult to apply usefully to experimental animals. The problem is not that declarative memory seems to imply an ability to declare one's knowledge verbally. Indeed, declarative memory includes mem-

ory for faces, spatial layouts, and other material that is declared by bringing a remembered image to mind rather than by verbalizing. The difficulty is that the term *declarative* is often linked to the notion of conscious memory. In the sections that follow, the idea of declarative memory is developed more fully in an attempt to make contact with similar ideas about memory systems derived from work with experimental animals. Declarative memory is also contrasted with a heterogeneous collection of nondeclarative (implicit) memory abilities, which are expressed only through performance and which are independent of the structures damaged in amnesia (Figure 5).

An additional point about the term *declarative* memory might be useful at this juncture. Many terms have been used to describe a particular kind of memory (e.g., *declarative, explicit, relational,* or *configural*), and many other terms have also been used to describe a kind (or kinds) that are dissociable from the first kind (e.g., *nondeclarative, implicit,* or *habit*). However, terms themselves are not the proper focus. If one considers the various biological and purely psychological concepts that have been used, it is striking that they sort themselves out in terms of ideas about what the hippocampus does and does not do in the service of memory. It should not be surprising that these terms place themselves on either side of a biologically meaningful boundary. The brain is the machinery that accomplishes memory, and history shows that other fundamental psychological distinctions have proved to be prominent in the organization of brain systems (e.g., short-term and long-term memory). Accordingly, the term *declarative* is used here to describe one kind of memory, but not with the idea that it is especially different from other terms. The more important point is that the terms *explicit memory* and *declarative memory*, when one considers the properties that have been associated with each, describe a biologically real component of memory that depends on particular structures and connections in the brain. Accordingly, it is to be expected that these terms have much in common with each other and with the terms *relational* and *configural*, which come from work with rats.

Recall, Recognition, and the Feeling of Familiarity

What kind of information is acquired as declarative memory and how is it best assessed? The assessment of memory has relied traditionally on two methods: free recall and recognition. In normal subjects, both recall and recognition are typically accompanied by a sense of familiarity about the past. Amnesic patients perform poorly on tests of recall and recognition, and they have a diminished feeling of familiarity as reflected in the low confidence ratings that they attach to their recognition choices. Recall and recognition have usually been taken as reflections of declarative memory (Tulving, 1983). This point of view leads to the expectation that recall and recognition should be proportionately impaired in amnesic patients and that confidence judgments (which assess awareness about the knowledge being reported) should be commensurate with the reduced level of memory performance.

Another point of view is that recognition-memory performance benefits not only from the ability to judge consciously whether a particular event has occurred recently or not, but that it also benefits from improved perceptual fluency (i.e., priming, a nonconscious process whereby recently encountered items are processed more quickly and accurately than new items; Gardiner, 1988; Jacoby & Dallas, 1981; Johnston, Dark, & Jacoby, 1985; Mandler, 1980). The idea is that subjects can ordinarily detect the facility or fluency with which they process a recently encountered test item and can then attribute this increased fluency to a recent occurrence of the item. A related idea, which also supposes that recognition performance depends greatly on nonconscious processes, is that subjects might sometimes be able to discriminate successfully between new and old items on a recognition test but be unable to reflect this

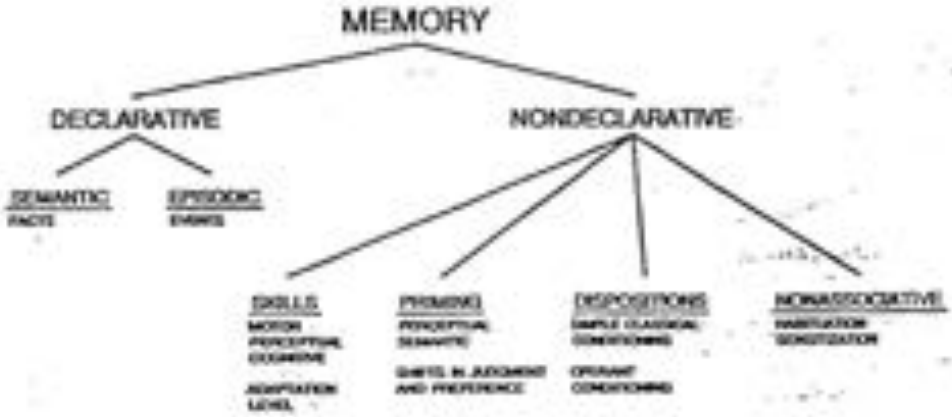

Figure 5. A memory taxonomy. (Declarative memory includes memory for facts and events and depends on the integrity of the hippocampus and related structures. Nondeclarative memory refers to a heterogeneous collection of distinct learning and memory abilities where performance changes but without affording access to the experience or experiences that caused the change. From "Neuropsychological Investigations of Memory and Amnesia: Findings From Humans and Nonhuman Primates," p. 437, by S. Zola-Morgan and L. R. Squire, 1990, in A. Diamond, *The Development and Neural Bases of Higher Cognitive Functions.* New York: New York Academy of Sciences. Copyright 1990 by the New York Academy of Sciences. Reprinted by permission.)

level of performance in verbal reports. For example, it has been suggested that amnesic patients should be able to exhibit successful recognition performance on a forced-choice test but would then report that they are in fact guessing (Weiskrantz, 1988). These ideas all lead to the prediction that the relationship among recall, recognition, and confidence ratings (for the recognition choices) should be different in amnesic patients than in normal subjects. For example, to the extent that recognition performance is based on perceptual fluency, which is intact in amnesia, recognition should be disproportionately spared relative to recall. In addition, to the extent that recognition performance is governed by nonconscious processes, then recognition choices should also be disproportionately spared relative to confidence ratings.

To address these issues, recall, forced-choice recognition, and confidence ratings for the recognition choices were tested at several different retention intervals (15 s to 8 weeks) in both normal subjects and amnesic patients (Haist, Shimamura, & Squire, in press). On all three measures the amnesic patients performed much worse than the normal subjects (Figure 6). Recall, recognition, and confidence ratings were similarly affected. Specifically, when the recognition scores of amnesic patients and control subjects were matched (the scores of amnesic patients tested from 15 s to 10 min after learning matched control scores obtained from 1 day to 2 weeks after learning), the free-recall scores and confidence ratings also matched.

These results suggest that recall, recognition, and feelings of familiarity are tightly linked functions of declarative memory. The crucial finding was that despite the fact that priming and other nonconscious memory processes are intact in amnesia, the recognition judgments of amnesic patients, and the confidence ratings attached to these judgments, were no better than would have been predicted from the recall scores. Several other studies with normal subjects have also suggested that recogni-

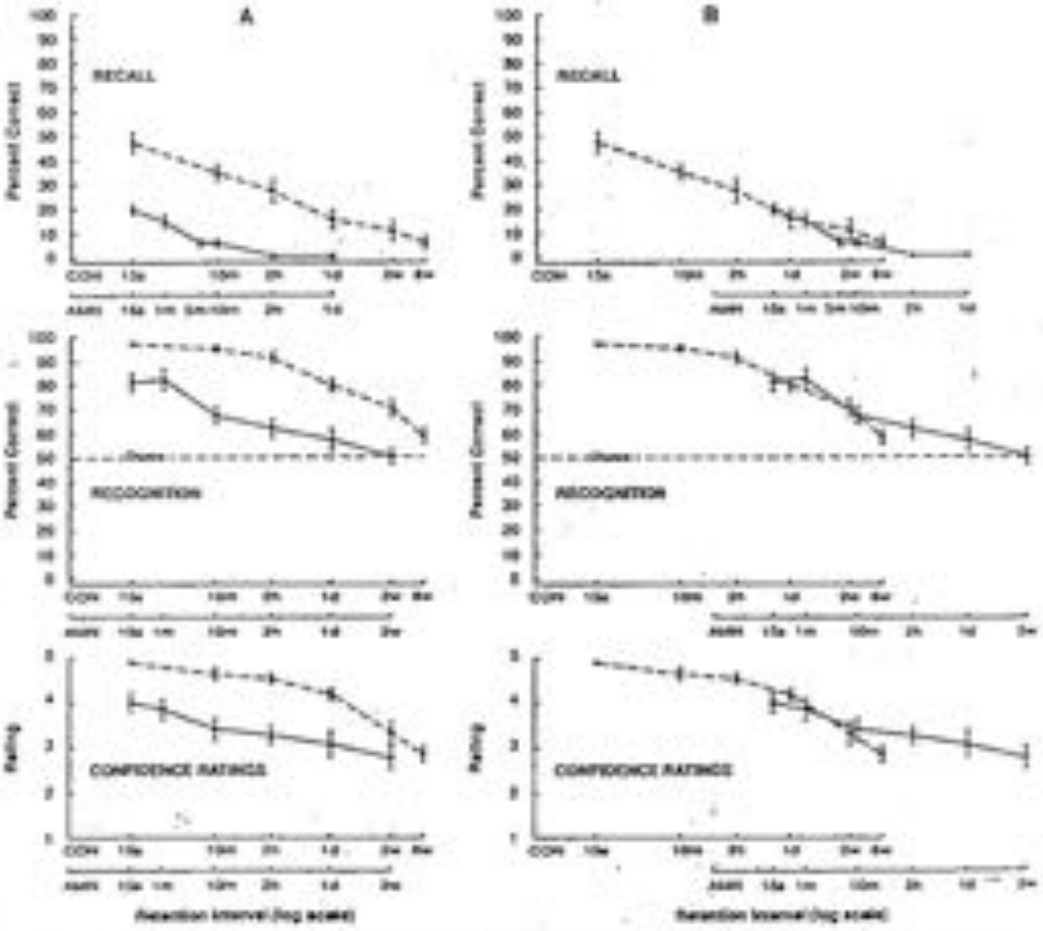

Figure 6. A: Free recall, two-choice recognition, and confidence ratings for the recognition choices for amnesic patients (AMN; solid lines) and control subjects (CON; dashed lines) who were given different 20-word lists and tested at each of the indicated retention intervals. B: When the recognition scores of the two groups were matched by redrawing the same data, the scores for free recall and for confidence ratings also matched. Error bars represent standard error of the mean. s = seconds; m = minutes; h = hours; d = days; w = weeks. (From "On the Relationship Between Recall and Recognition Memory" by F. Haist, A. P. Shimamura, and L. R. Squire, in press, *Journal of Experimental Psychology: Learning, Memory, and Cognition, 18*. Figures 1 and 2. Copyright 1992 by the American Psychological Association.)

sion memory need not benefit from priming; that is, recognition can be at chance levels despite the fact that other influences of stimuli on behavior can be detected (Bonnano & Stillings, 1986; Kunst-Wilson & Zajonc, 1980; Mandler, Nakamura, & Van Zandt, 1987; Seamon, Brody & Kauff, 1983; Seamon, Marsh, & Brody, 1984; Squire, Shimamura, & Graf, 1985).

Two previously published reports concluded that recall can be disproportionately impaired in amnesia (Hirst, Johnson, Phelps, Risse, & Volpe, 1986; Hirst, Johnson, Phelps, & Volpe, 1988). In these studies, recall and recognition were compared at only a single point, and recall and recognition tests were given sequentially in the same session rather than in separate sessions. However, we were unable to replicate this finding using the same experimental design (Haist, Shimamura, & Squire, in press). The different findings did not reflect differences in the severity of amnesia. While it remains unclear what factors do account for the different findings, one possibility is that variations in the locus of pathology are important. For example, damage to the frontal lobes could be expected to affect recall more than recognition (Jetter, Poser, Freeman, & Markowitsch, 1986), presumably because recall is affected more than recognition by impaired search strategies and impaired ability to organize incoming information.

In summary, a test of alternative views about recall and recognition was arranged by studying amnesic patients. If either recognition judgments or confidence ratings (i.e., feelings of familiarity) were significantly supported by processes that are intact in amnesia (e.g., nonconscious memory processes that rely on increased facility of perceptual processing), then recall scores should be disproportionately impaired in amnesia relative to either recognition scores or confidence ratings. However, this effect was not observed. Instead, recall, recognition, and familiarity judgments appear to be tightly linked functions of declarative memory and similarly dependent on the brain systems damaged in amnesia. Other recent studies of normal subjects agree that recognition memory need not benefit from perceptual fluency (Hayman & Tulving, 1989; Watkins & Gibson, 1988). Johnston, Hawley, and Elliott (1991) concluded that perceptual fluency may sometimes contribute to recognition performance but that its contribution is small when explicit, conscious memory is readily available. Thus, in a real-world situation where material is relatively familiar (i.e., recognition performance is well above chance level) and decision time is uncontrolled, recognition performance may draw little benefit from implicit memory.

Spatial Memory

One view about the selective role of the hippocampus in memory, derived especially from studies of rats, is that it is involved in memory for spatial information (O'Keefe & Nadel, 1978). According to this view, the hippocampus is a memory system that stores information about nonegocentric (viewpoint-independent) space. This view describes the function of the hippocampus too narrowly. Although many of the tasks sensitive to hippocampal lesions are tasks of spatial memory, it is also clear that hippocampal lesions impair nonspatial memory. For example, lesions of hippocampus or related structures impair the ability of rats to learn odor discriminations (Eichenbaum, Fagan, Mathews, & Cohen, 1988), timing tasks (Meck, Church, & Olton, 1984), and configural discriminations that involve unique combinations of auditory or visual stimuli (Rudy & Sutherland, 1989). In monkeys, lesions of the hippocampal formation impair recognition memory for visual objects, simple-object-discrimination tasks, and concurrent-discrimination learning for objects (Zola-Morgan et al., 1989a). None of these tasks has an obvious spatial component.

These findings in rats and monkeys are in agreement with findings from amnesic patients with hippocampal damage. The patients do lose their way, and they cannot learn or remember spatial layouts, but they also forget prose passages, tactual impressions, odors, faces, and melodies. In amnesia, spatial memory impairment is just one aspect of a broad impairment in (declarative) memory (Squire, 1979).

A recent study in monkeys raised the possibility that, whereas memory is broadly affected following hippocampal damage, spatial memory ability might be disproportionally impaired (Parkinson, Murray, & Mishkin, 1988). In that study, monkeys with hippocampal formation lesions were unable to learn object-place associations. The impairment was much more severe than was observed in an earlier study of recognition memory for visual objects (Mishkin, 1978). However, these two tasks (object-place memory and visual recognition memory) differ from each other in important ways, quite apart from the fact that one of the tasks is spatial and the other is not. For example, in the object-place task the location of an object must be recalled in the absence of external cues. The monkey is confronted with two identical objects, placed in two familiar locations, and must associate the object to the spatial location that was recently rewarded. By contrast, the visual object task is a task of recognition. The monkey is confronted with two different objects (a novel one and a familiar one) and must recognize which one was recently presented. Accordingly, it is possible that monkeys failed the object-place task because recall is more difficult than recognition, not because the object-place task requires spatial memory.

The possibility that hippocampal lesions might impair spatial memory disproportionally more than nonspatial memory has been tested directly in amnesic patients, including patients with confirmed damage to the hippocampus (Cave & Squire, 1991). Fourteen amnesic patients inspected an array of 16 toy objects (cf. Smith & Milner, 1981) and were subsequently asked to recall the objects, recognize their names on a multiple-choice test, and then reconstruct the array by placing the objects in their original locations. Normal subjects took the same tests, at one of several different retention intervals (from 5 min to 5 weeks after learning), so that their performance on the object-memory tasks could be equated with that of the patients. The results were that, when performance of the amnesic patients on the two object-memory tests was matched to the object-memory performance of control subjects, spatial memory performance was also equivalent for amnesic patients and control subjects. That is, the impairment in spatial memory was proportional to the impairment in object recall and object recognition.

This result might seem in conflict with earlier studies in rats with hippocampal lesions, which have reported that spatial

memory is impaired (e.g., radial maze performance using room cues) and that nonspatial memory is unimpaired (e.g., radial maze performance with relevant visual cues in each arm). For many years, it was possible to interpret this pattern of results as favoring an important role for the hippocampus in spatial memory functions. However, more recent studies of rats (Eichenbaum et al., 1989; Packard, Hirsh, & White, 1989; Sutherland & Rudy, 1989), monkeys (Mishkin et al., 1984; Zola-Morgan & Squire, 1984), and humans (Cohen & Squire, 1980; Schacter, 1987; Weiskrantz, 1987) with hippocampal lesions have led to a different interpretation; namely, performance is spared on some nonspatial tasks not because they are nonspatial but because performance on these tasks depends on a broader class of memory abilities (here termed *nondeclarative*; other terms that refer to this broad class include *habits*, *simple associations*, and *implicit memory*). Nonspatial tasks that are spared after hippocampal lesions include simple win–stay tasks, as when rats must gradually strengthen a stimulus–response association, and some visual discrimination habits where learning is gradual across trials. This interpretation accommodates the finding that performance on both spatial and nonspatial tasks can be impaired by hippocampal lesions by proposing that all such tasks depend on a particular kind of memory (here termed *declarative*). Thus, in humans and other mammals, the hippocampus is not functioning in a particularly spatial way. Spatial memory simply provides one good example of the kind of memory that depends on the hippocampus.

The Role of the Hippocampal Formation: Establishing Conjunctions

A consideration of the anatomical and physiological organization of the hippocampus suggests that it functions as a device for forming conjunctions between ordinarily unrelated events (Squire, Shimamura, & Amaral, 1989). One possible associative device is long-term potentiation (LTP), a rapid-developing and long-lasting form of synaptic plasticity (Bliss & Lomo, 1973; Gustafsson & Wigstrom, 1988). LTP is cooperative: it depends on convergent inputs occurring nearly simultaneously, and it provides a mechanism by which conjunctions can be formed and stored. Similar proposals identify the hippocampus as the storage site for a simple memory, a summary sketch, a gross trace, an index, a device for constructing unique configurations among stimuli, or for collating widely stored pieces of experience (Halgren, 1984; Marr, 1971; McNaughton & Nadel, 1990; Moscovitch, 1989; Rolls, 1990; Sutherland & Rudy, 1989; Teyler & Discenna, 1986). In psychological terms, the hippocampus contributes to the forming of new relationships, such as those established when associating stimuli with their spatial and temporal context (thus representing a new episode) or those established when associating a fact with the semantic context to which it belongs (thus representing a new concept).

It is clear that the hippocampal formation must perform a critical function at the time of learning if declarative memory is to be established in an enduring and usable way. In the case of transient amnesic episodes, the events that occur during the period of anterograde amnesia do not subsequently reappear in memory after recovery from amnesia. New learning becomes possible, but events from the amnesic episode do not return.

Because memories do not return after transient amnesic episodes, it appears that, in the absence of the hippocampus, representations that had been established in short-term memory are literally lost, become disorganized, or achieve some abnormal fate. In this sense, it seems reasonable to suppose that the hippocampus is needed for memory storage to occur. Yet, one could also propose that its role is to permit retrieval by establishing relationships at the time of learning with distributed neocortical storage sites. However, because neural plasticity is prominent in the hippocampus, in the form of a mechanism that seems well suited for forming and storing conjunctions (LTP), it seems more reasonable to view the hippocampus as a site that, together with other sites, actually stores an experience. Also, a purely retrieval view of hippocampal function cannot be correct because chronic amnesic patients do not recover from their retrograde amnesia as time passes, even though normally stored memories do become gradually independent of the hippocampus (see section on retrograde amnesia).

Configural Associations

One view that is similar to what is being proposed here is that the hippocampus is essential for memory tasks that require the development of configural as opposed to simple associations (Sutherland & Rudy, 1989). Certain operations, such as the exclusive-OR operation, cannot be accomplished by strengthening or weakening simple associations between stimulus and response elements. It has been proposed that the hippocampus is required for those kinds of learning in which unique combinations of stimuli must be remembered. The clearest demonstration of this idea is the report that rats with hippocampal lesions could not solve a negative patterning discrimination problem. Specifically, they did not learn to discriminate correctly in a case where either a light (L) or a tone (T) was rewarded, but the light–tone compound stimulus (LT) was unrewarded (Rudy & Sutherland, 1989).

As the authors of this proposal suggested, this idea has many points of contact with other views (Hirsh, 1974; Mishkin et al., 1984; Wickelgren, 1979). What these views share is a distinction between a simpler kind of learning that is independent of the hippocampus and that is reminiscent of the associative learning discussed by Hull (1942) and Spence (1936) and a more cognitive kind of learning of the kind discussed by Tolman (1948). Whereas this perspective seems generally correct, the configural hypothesis is incomplete in an important respect. The difficulty is that many tasks admit to more than one strategy. How does one know when an animal has learned by acquiring a configural association? One approach is to define *configural* according to a logical analysis of tasks. A task is usually identified as *configural* when the individual elements of a task are equally often reinforced and nonreinforced and when a unique combination of stimuli must therefore be learned to solve the problem. However, some tasks that are configural in this sense can be learned successfully by rats with hippocampal lesions (Gallagher & Holland, 1992; Whishaw & Tomie, 1991). For example, operated rats successfully relearned a preoperatively trained problem (although not at a normal rate) involving two tactile stimuli (A and B) and two olfactory stimuli (C and D). These were paired, such that AC was rewarded, AD was

unrewarded, BC was unrewarded, and BD was rewarded (Whishaw & Tomie, 1991). It may be the case that, rather than treat some compound stimuli (or some conditional relationship) as unique configurations of other stimuli, rats can simply treat each stimulus or stimulus combination as a separate problem (i.e., a distinct group of stimuli) and acquire independent conditional reactions for each one of them.

Relational and Flexible Memory

One way in which the original notion of declarative memory is making useful contact with studies of experimental animals is found in the idea that the hippocampus is essential for establishing flexible representations on the basis of relationships among stimuli (Eichenbaum et al., 1988). Whereas configural associations do not imply either flexibility or inflexibility, declarative memory entails a specific view of this issue (Cohen, 1984; Squire, 1987). By this view, the hippocampus, and the system to which it belongs, is essential for acquiring information about relationships, combinations, and conjunctions among stimuli, such that the resulting representation is flexible and accessible to multiple response systems.

This idea is still insufficiently formal and quantitative. Moreover, it remains difficult to predict beforehand which memory system will be engaged. Humans are overwhelmingly declarative; that is, they are memorizers and will readily engage hippocampus-dependent memory. Rats will readily adopt a simple associational strategy. Thus, it is difficult to know when a rat, in the presence of a light and a tone, for example, will simply form a conditioned response to the compound cue and when the rat will form a relational, hippocampus-dependent memory. However, the key idea is that the two kinds of memory, once acquired, have different characteristics.

In one study, rats with fornix lesions and sham-operated rats were trained on a series of simultaneous olfactory discrimination problems (Eichenbaum et al., 1989). Overall, the rats with fornix lesions were impaired at acquiring the discrimination problems, but all the animals were eventually able to reach a high level of performance on at least two problems. When two problems had been learned successfully (here termed A+B− and C+D−), rats were retrained to perform the two problems concurrently. Then, during continued training, occasional probe trials were given in which the stimuli were recombined (A+D− and C+B−). Control rats and fornix rats performed similarly during the regular, familiar trials (82.8% correct vs. 79.2% correct). The control rats performed nearly as well during the probe trials (from 75% to 80% correct) as during the regular trials. By contrast, the fornix rats were severely impaired (from 50% to 63% correct during the first 50 probe trials). Thus, the unoperated animals had no difficulty responding to a new stimulus combination, because they could make use of the information that had been acquired previously about the reward value of the two elements that comprised each combination. The rats with fornix lesions behaved inflexibly, as if the recombined stimuli constituted two new problems.

The same conclusion was reached in a different study involving monkeys (Saunders & Weiskrantz, 1989). Four normal monkeys and four monkeys with bilateral fornix lesions, or combined lesions of the hippocampal formation, fornix, and mammillary nuclei, received training in five stages until they were able to acquire object–object associations. The task involved eight different object pairs, which were constructed by pairing four different objects and varying their left–right position (AB, BA, AC, CA, CD, DC, BD, and DB). Two of these pairs were always presented together for discrimination training, and food reward was placed beneath each member of the correct pair. Training continued until in the final stages any one of the positive object pairs (AB+, BA+, or CD+, DC+) could be discriminated from any of the negative pairs (AC−, CA−, or BD−, DB−). Operated monkeys and normal monkeys acquired the object–object associations in about the same number of trials. Correct performance depended on the monkey's having learned to respond on the basis of the two objects in the pair (i.e., *A* was correct only when it was paired with *B*, not when it was paired with *C*; *D* was correct when it was paired with *C*, not when it was paired with *B*).

After the object pairs had been learned, monkeys were given a performance test designed to determine what kind of knowledge the monkeys had acquired about the associations. For the performance test, the objects were separated and appeared as single objects rather than as pairs. For each trial, one object (*A* or *D*) was presented over the center food well, and two others (*B* and *C*) were presented over the two most lateral wells. The monkey was rewarded if it chose from the two lateral objects (*B* and *C*) the one that had been paired with the center object throughout training. Thus, if *A* was presented over the central food well, *B* was the correct choice. If *D* was presented over the central food well, then *C* was the correct choice. During 32 performance trials, unoperated monkeys performed at about 70% correct, but the operated monkeys performed at chance. The results show that normal monkeys had acquired information about which objects had appeared together during learning, and they could express this knowledge in a novel situation. By contrast, the operated monkeys appeared to have acquired only conditional associations about the stimuli and the rewards associated with them. Accordingly, they were unable to express this knowledge outside of the context in which it was originally acquired.

These two studies provide direct evidence for the idea that hippocampus-dependent and hippocampus-independent memory have different characteristics (for a consideration of this same issue with amnesic patients, see Glisky, Schacter, & Tulving, 1986a; 1986b; Shimamura & Squire, 1988). The following sections consider further the characteristics of the kind of memory that is independent of the hippocampus. One important finding to emerge from this work is that declarative and nondeclarative memory not only have different characteristics but also depend on different brain structures.

Nondeclarative (Implicit) Memory

The term *procedural memory* was traditionally used to contrast with declarative memory (Winograd, 1975). *Procedural memory* aptly describes the knowledge acquired during skill learning, but it is not clear that this same term is useful for the many examples of learning and memory now known to be independent of the hippocampus. The more neutral term *nondeclarative* was subsequently introduced to describe this collec-

tion of memory abilities (Squire & Zola-Morgan, 1988). The term *implicit memory* (Reber, 1967; Schacter, 1987) has a similar meaning. Nondeclarative memory includes skillful behavior or habits (perceptuo-motor, perceptual, and cognitive skills), simple conditioning (including emotional learning), the phenomenon of priming, and other instances where experience changes the facility for operating in the world but without affording conscious access to past episodes. Whereas declarative memory concerns recollection, nondeclarative memory concerns behavioral change. In nondeclarative memory, information is acquired as changes within specific perceptual or response systems, independently of memory for the prior encounters that led to behavioral change.

Different brain systems appear to be involved in these kinds of learning, and in correspondence with this idea, dissociations have been obtained following brain lesions where, for example, one kind of nondeclarative memory is impaired and another is intact (Butters, Heindel, & Salmon, 1990; Heindel, Salmon, Shults, Walicke, & Butters, 1989; Saint-Cyr, Taylor, & Lang, 1988; Thompson, 1986). Evidence suggests that skill learning and habits depend on the integrity of the neostriatum (Heindel, Butters, & Salmon, 1988; Heindel et al., 1989; Packard et al., 1989; Saint-Cyr et al., 1988; Wang, Aigner, & Mishkin, 1990), conditioning of skeletal musculature depends on the cerebellum (Thompson, 1986), emotional conditioning depends on the amygdala (Davis, 1986; LeDoux, 1987), and some kinds of priming depend on early-stage processing systems in posterior neocortex (Squire, Ojemann, Miezin, Petersen, Videen, & Raichle, in press).

Skills and habits. Skills in human subjects are typically acquired gradually and often without noticeable conscious memory of what kind of information has been acquired. For example, motor skills can be acquired and maintained without subjects being aware of what they have learned to do. At the same time, it is often difficult to know when declarative memory (i.e., explicit attempts to recall or recognize previously presented material) makes a substantial contribution to skilled performance. Amnesia provides a useful way to explore this issue, because whenever declarative memory contributes to performance amnesic patients should perform less well than control subjects. Thus, a finding that patients perform entirely normally provides particularly strong evidence that performance does not depend materially on declarative memory.

Studies of amnesic patients show that motor skills (Brooks & Baddeley, 1976), perceptuo-motor skills (Nissen & Bullemer, 1987), perceptual skills (Cohen & Squire, 1980), and early-stage cognitive skill learning (Squire & Frambach, 1990) can be intact in amnesia and independent of the brain structures damaged in amnesia. Furthermore, the skills acquired by amnesic patients can reflect highly specific information about the items that were encountered (Moscovitch, Winocur, & McLachlan, 1986; Musen, Shimamura, & Squire, 1990; Figure 7). The skills can also be based on novel information. For example, amnesic patients were able to acquire normally a reading skill for regularly repeating nonwords (Musen & Squire, 1991; Figure 7).

A final example of preserved memory ability in amnesic patients, which is likely based on skill learning, is the phenomenon of adaptation-level effects for the perceived heaviness of weights (Benzing & Squire, 1989). An experience lifting 40

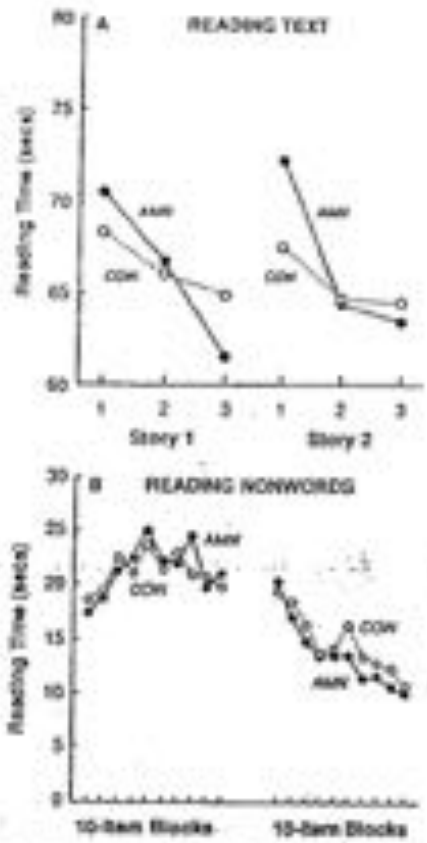

Figure 7. Intact learning by amnesic patients as measured by improved reading times. A: Text-specific reading skill. A story was read three times slowed, followed immediately by three readings of a second story. B: Reading skill for nonwords. Subjects read either a 100-item list of unique (Panel A) nonwords or a 100-item list in which five nonwords were repeated 20 times each (Panel B). AMN = amnesic patients; CON = control subjects. Panel A from "Intact Text-Specific Reading Skill in Amnesia" by G. Musen, A. P. Shimamura, and L. R. Squire, 1990, *Journal of Experimental Psychology: Learning, Memory, and Cognition, 6*, p. 1071. Copyright 1990 by the American Psychological Association. Reprinted by permission. Panel B from "Normal Acquisition of Novel Verbal Information in Amnesia" by G. Musen and L. R. Squire, 1991, *Journal of Experimental Psychology: Learning, Memory, and Cognition, 17*, p. 1098. Copyright 1991 by the American Psychological Association. Adapted by permission.

small weights with one hand influenced judgments of a second group of 10 weights 20 to 25 min later, using the other hand. The influence was as strong in amnesic patients as in normal subjects, although the amnesic patients were severely impaired at recollecting their earlier experience with the weights. Recent findings with other neurological patients suggest that this adaptation-level effect is based on acquiring a motor program for lifting, which is appropriate to the first set of weights but is then misapplied to the second set of weights. Patients with Huntington's disease, who are deficient at motor-skill learning, did not exhibit this adaptation-level effect, but patients with Alzheimer's disease performed like normal subjects (Heindel, Salmon, & Butters, 1991).

In nonhuman primates, motor-skill and perceptual skill

learning also occurs normally despite large bilateral lesions that include the hippocampal formation (Zola-Morgan & Squire, 1984). In addition, associative habits can be acquired normally following medial temporal lobe lesions; for example, the 24-hr concurrent-discrimination task (Malamut et al., 1984). In this task, monkeys are presented each day with 20 object pairs, and one object in each pair is always the correct one. Monkeys see each pair only once each day, and over many days they learn to choose the correct object of each pair. Finally, in rats, performance in the conventional radial maze task was unimpaired after fornix lesions when the animals had to learn to associate specific arms with reward (a win–stay strategy) (Packard et al., 1989). By contrast, performance was impaired in the same apparatus when a win–shift strategy was required. In the win–shift task, animals can obtain one reward in each arm of the maze, and they learn to visit each arm without repeating entries to already visited arms.

Recent work shows that some habitlike tasks that are intact in animals with hippocampal lesions are impaired by lesions of the caudate nucleus (the win–stay task just described, Packard et al., 1989; the 24-hr concurrent task, Wang et al., 1990). Thus, a different neural system is necessary for the learning of these tasks than is necessary for tasks of declarative memory. For example, in the monkey, inferotemporal neocortex (area TE) is essential for both visual recognition memory and for the 24-hr concurrent task (Mishkin, 1982; Phillips, Malamut, Bachevalier, & Mishkin, 1988). As discussed earlier, recognition memory, as measured in the delayed-nonmatching-to-sample task, is dependent on the hippocampus and related structures. Recognition memory thus requires that inferotemporal cortex operate in concert with the hippocampal system. The 24-hr concurrent task, a task of habit memory, requires that inferotemporal cortex operate in concert with the caudate nucleus.

Especially because skills and habits can be complex, it is often difficult to determine beforehand whether they involve declarative memory to a substantial degree. Studies of normal subjects do not easily settle the issue. Consider, for example, the learning of artificial grammars by normal subjects, which is considered on the one hand to be incremental, nonconscious, and implicit (Reber, 1967, 1976), but which has also been considered to proceed by the imperfect learning of partial solutions that use explicit-memory strategies and explicit memory for the exemplars (Dulaney, Carlson, & Dewey, 1984). Recent studies of amnesic patients have illuminated this issue. Amnesic patients were able to classify letter strings according to the rules of an artificial grammar as well as control subjects (Knowlton, Ramus, & Squire, in press). However, the patients were impaired at recognizing the exemplars that had been used to teach the rules. These results do not support models in which classification judgments occur only by direct and explicit comparison with stored exemplars (Hintzman, 1986; McClelland & Rumelhart, 1985).

The results argue instead for the participation of at least two memory systems in classification learning: one system stores the exemplars that are presented to the subject, and a second system allows for the gradual development of rule-based behavior as exemplars are presented. The first system depends on the hippocampus and related structures and provides for exemplar memory. The second system provides more abstract information, which is constructed out of the exemplars. In keeping with recent suggestions that certain kinds of habit learning are impaired by neostriatal lesions (Packard et al., 1989; Wang et al., 1990), an interesting possibility is that artificial grammar learning in particular, and classification and prototype learning in general, depend on the neostriatum.

Conditioning The gradual acquisition of dispositions by which subjects interact with the world can also occur independently of the hippocampal formation. For example, amnesic patients exhibited good classical conditioning of the eyeblink despite poor memory for the events of the training session (Daum, Channon, & Canavar, 1989; Weiskrantz & Warrington, 1979). However, normal subjects have not yet been tested concurrently to show that conditioning in the patients is entirely normal. The data in experimental animals are somewhat clearer. Rabbits with hippocampal lesions showed normal acquisition of the nictitating membrane reflex (Solomon & Moore, 1975). In addition, heart-rate conditioning and skeletal measures of conditioned fear can be acquired in animals with hippocampal lesions (LeDoux, 1987; Powell & Buchanan, 1980; Rickert, Bennett, Lane, & French, 1978). Thus, the ability to acquire many kinds of simple conditioned reactions occurs independently of the hippocampus. However, in more complicated conditioning paradigms, as when effects of context are important, the hippocampus can make an essential contribution to performance (Berger & Orr, 1983; Moyer, Deyo, & Disterhoft, 1990; Rickert et al., 1978; Thompson, 1983).

Priming Priming refers to an increased facility for detecting or identifying words or other stimuli as a result of their prior presentation (Graf et al., 1984; Shimamura, 1986; Tulving & Schacter, 1990). Priming can involve the acquisition of new information, not simply the activation of preexisting knowledge. Earlier studies suggested that amnesic patients do not show priming effects for nonwords and that priming therefore depends on activation of preexisting representations (Cermak, Talbot, Chandler, & Wolbarst, 1985; Diamond & Rozin, 1984). However, it now seems likely that the normal subjects in these studies were able to outperform the patients by relying on declarative memory strategies. In a study designed to reduce the possibility of using declarative memory strategies, amnesic patients exhibited fully intact priming for nonwords (Haist, Musen, & Squire, 1991). Other recent studies have reached a similar conclusion, namely that priming effects can occur for novel material and that amnesic patients exhibit such effects as readily as normal subjects. For example, normal subjects and amnesic patients exhibited priming of unfamiliar visual objects, which was independent of recognition-memory performance (Schacter, Cooper, & Delaney, 1990; Schacter, Cooper, Tharan, & Rubens, 1991). In addition, normal subjects and amnesic patients improved their ability to reproduce novel line patterns independently of their ability to recognize the patterns as having been presented previously (Musen & Squire, in press; Musen & Treisman, 1990). The severely amnesic patient H. M. was also reported to exhibit this effect (Gabrieli, Milberg, Keane, & Corkin, 1990).

In another study, amnesic patients developed a normal preference for novel melodies that they had heard, although the patients were poor at recognizing the melodies as ones that had

been presented (Johnson, Kim, & Risse, 1985). In addition, amnesic patients showed as large a tendency as normal subjects to judge proper names as famous, if the names had recently been presented (Squire & McKee, 1992). The facilitatory effect of prior study was as large for nonfamous names (e.g., Ennis Lekovic) as for famous names (e.g., Olga Korbut), suggesting that the effect did not require a preexisting representation. The amnesic patients were impaired at recognizing which names had been presented. It seems plausible that the fame judgment effect, originally studied in normal subjects (Jacoby, Woloshyn, & Kelley, 1989; Neeley & Payne, 1983), is based on word priming. If so, priming not only improves the ability to identify novel stimuli but also alters judgments and preferences involving the same stimuli. Such effects are also reminiscent of demonstrations in normal subjects that judgments and preferences for novel stimuli can be influenced independently of the ability to recognize the stimuli as familiar (Bonnano & Stillings, 1986; Kunst-Wilson & Zajonc, 1980; Mandler et al., 1987).

Recent work suggests that one kind of priming (what has been termed *direct* or *repetition* priming) occurs as changes in early-stage perceptual processing systems in posterior cortex, before conceptual or semantic analysis is carried out and before the involvement of the hippocampal formation and the development of declarative memory. In repetition priming, a stimulus item must simply be detected or identified. Conceptual or semantic priming depends on the meaning of the stimulus (for additional discussion of this distinction, see Tulving & Schacter, 1990). A recent functional anatomical study of word-stem completion priming using positron emission tomography (PET) provided direct evidence for the relevance of posterior cortex to repetition priming (Squire et al., in press). Words were first presented visually in center field in uppercase letters, and word stems were then presented in the center field, also in uppercase letters, with instructions to complete the word stems to form the first word to come to mind. A reduction of blood flow occurred in a region of right extrastriate cortex during word-stem completion priming, compared with a baseline condition in which priming could not occur because none of the possible completions had been presented. Thus, for a time after a stimulus has been presented, less neural activity may be required to process the same stimulus.

The right hemispheric locus of this change is consistent with related findings from divided visual field studies showing that word-stem completion priming can be supported by form-specific mechanisms in the right cerebral hemisphere. Words were presented for study at a central fixation point, and word stems were later presented in either the left or right visual field (Marsolek, Kosslyn, & Squire, in press). A left-visual field (right-hemisphere) advantage occurred for word-stem completion priming, but only when items were presented at study and test in the same modality and in the same letter case.

Other suggestions about priming include the idea that repetition priming of words might occur as changes in a left posterior word-form system, presumably a system specialized for the abstract processing of words rather than form-specific processing, and that priming of visual objects might occur as changes in a right-hemisphere, structural description system (Schacter, 1990a; Tulving & Schacter, 1990). Whereas one might worry that such ideas will lead to proposing a new memory system for each new task (Roediger, 1990), another point of view is that a large number of cortical systems are in fact involved in priming. If priming reflects changes in the neural systems that are ordinarily involved in perception, then priming may occur in each of the multiple, separate cortical processing regions that have been identified and that remain to be identified.

In the primate visual system alone, as many as 30 areas have been specified on the basis of function, connectivity, and laminar organization (Felleman & Van Essen, 1991; Kaas, 1989; Zeki & Shipp, 1988). Priming may occur in any of these areas. Which perceptual areas and which hemisphere support priming can be expected to vary depending on the task, the stimulus materials, and the extent to which form-specific or more abstract processing mechanisms are engaged (for further discussion of this distinction, see Marsolek et al., in press).

Studies of normal subjects and amnesic patients show that priming is quite specific compared with declarative memory. Thus, priming effects are readily diminished by altering the physical features of the original items. Declarative memory is much less sensitive to the similarity between the physical features of study and test items. The specificity of priming effects is demonstrated by the fact that priming effects are diminished by changing the physical form of an item (for objects, changing from one to another picture of the same object [Bartram, 1974; Biederman & Cooper, 1991, in press; Cave & Squire, in press; Jacoby, Baker, & Brooks, 1989] or from a picture of an object to the printed name of the object [Weldon & Roediger, 1987; Winnick & Daniel, 1970]; for words, changing the modality of item presentation [Graf, Shimamura, & Squire, 1985], changing typeface [Jacoby & Hayman, 1987; Marsolek et al., in press], or otherwise greatly changing the physical appearance of visually presented words [Graf & Ryan, 1990; Jacoby & Hayman, 1987; Roediger & Blaxton, 1987]).

At the same time, precisely the same word form or object need not be presented at study and test (i.e., with exactly the same contours or in exactly the same position in the visual field, for example) for priming to occur at full strength (Biederman & Cooper, 1991, in press; Graf & Ryan, 1990; for review, see Schacter, Delaney, & Merikle, 1990). These results suggest that priming occurs in systems that have extracted some surface, physical features and that are already processing a somewhat abstract version of the stimulus. Nevertheless, priming effects are strongly determined by structural features of the perceptual object that was originally presented. The extent of priming and the importance of study-item–test-item compatibility can be expected to vary, depending on which hemisphere supports the phenomenon and which cortical systems are involved. One clear example of this point came from the visual field studies of normal subjects mentioned earlier (Marsolek et al., in press). When word stems were presented to the left hemisphere, word-completion priming was not affected by changes in letter case. When the word stems were presented to the right hemisphere, priming was diminished by changing the letter case.

Novel Associations in Implicit Memory

Table 4 illustrates the kinds of learning that can be supported by nondeclarative (implicit) memory. The Table shows that im-

Table 4
Kinds of Information That Can Be Supported by Nondeclarative (Implicit) Memory and Acquired by Amnesic Patients

Specific information	Novel information	New associations
	One-trial learning	
Word identification (Cermak, Talbot, Chandler, & Wolbarst, 1985)	Novel melodies (Johnson, Kim, & Risse, 1985)	—
Word completion (Graf, Squire, & Mandler, 1984)	Nonfamous names (Squire & McKee, 1992)	—
Modality-sensitive priming (Graf, Shimamura, & Squire, 1985)	Unfamiliar objects (Schacter, Cooper, & Delaney, 1991)	—
	Nonwords (Haist, Shimamura, & Squire, in press)	
	Multiple-trial learning	
Text-specific reading skill (Musen, Shimamura, & Squire, 1990)	Reading nonwords (Musen & Squire, 1991)	Word pairs (Musen & Squire, 1990)
Serial-reaction skill (Nissen & Bullemer, 1987)	—	Classical conditioning (Daum, Channon, & Canavan, 1989; Weiskrantz & Warrington, 1979)

Note. References are to representative studies and are not exhaustive.

plicit memory can support many of the same kinds of learning that are supported by declarative memory and that are dependent on the hippocampus. For example, the acquired information can be specific to presented words or objects. Learning is not limited to the acquisition of generic knowledge that is acquired, for example, by averaging information across trials. In addition, entirely novel information can be acquired. These characteristics have led some to suggest that declarative and nondeclarative memory reflect different processes by which the same underlying information is accessed (Jacoby, 1988; Roediger, 1990). However, as discussed here and elsewhere (Sherry & Schacter, 1987; Squire, 1987; Tulving & Schacter, 1990), declarative and nondeclarative memory are not as similar as this list might suggest. The biological facts, as summarized in this review, provide an account in terms of distinct brain systems subserving different kinds of memory, each with different properties.

Table 4 also identifies a kind of learning that is readily supported by declarative memory but can scarcely be accomplished at all by nondeclarative (implicit) memory. The work leading to this conclusion concerns the ability of amnesic patients and normal subjects to acquire novel associations. One line of work began with reports that normal subjects and some amnesic patients exhibited greater word-completion priming when the word stem presented at test was paired with a previously associated target word (e.g., study BELL–CRADLE, test BELL–CRA; Graf & Schacter, 1985). However, subsequent studies found that amnesic patients do not exhibit this effect reliably (Cermak, Bleich, & Blackford, 1988; Mayes & Gooding, 1989; Schacter & Graf, 1986; Shimamura & Squire, 1989). Although separate studies with normal subjects showed unequivocally that priming of new associations is dissociable from other measures of declarative memory (Graf & Schacter, 1987; Schacter & Graf, 1989), the fact that amnesic patients are nevertheless impaired suggests that a significant part of this effect depends on declarative memory. To exhibit priming of new associations between two semantically unrelated words, subjects may need to access a link between the two words that was formed declaratively at the time of study (see Shimamura & Squire, 1989).

A second line of work began with the report that memory-impaired patients could establish novel associations between words in a single trial (Moscovitch et al., 1986). Word pairs were first presented one at a time. Then subjects were asked to read as quickly as possible three different kinds of material: the same word pairs that had already been presented, a new set of word pairs, or the same word pairs presented in a recombined fashion. Evidence that an association between the word pairs had been acquired would be found in slower reading times for the recombined word pairs, as compared with the old word pairs. This result was reported in the initial study by Moscovitch et al. (1986), but the effect was a small one, and it has proven difficult to replicate. In recent work based on the same paradigm, word pairs were presented either once or multiple times, and subjects were instructed to read them and to attempt to form a link between the members of each pair (Musen & Squire, 1990). The results were generally the same for amnesic patients and control subjects. Even after a single trial, old pairs were read more quickly than new pairs, which reflects a priming effect for familiar words. However, in three separate experiments, recombined word pairs were read just as quickly as old word pairs. That is, there was no disruptive effect of recombining the words, indicating that no effective association had been formed between them. Accordingly, no learning of new associations occurred in a single trial, as measured by reading speed. The results were different when word pairs were presented multiple times. After reading word pairs several times in rapid

succession (22 times in one experiment), recombined pairs were read significantly more slowly than old pairs, although the effect was numerically small.

These results are consistent with the idea that nondeclarative (implicit) learning is specialized for incremental, cumulative change and that new associations can be acquired implicitly but only after many repetitions. Consider a typical task of associative learning, such as paired associate learning, using explicit instructions to memorize. Amnesic patients with hippocampal damage should eventually be able to acquire new associations through repetition, as in the development of a habit. However, their rate of learning would be grossly abnormal in comparison with normal subjects, and the acquired knowledge should be abnormal in other respects as well (for relevant studies, see Glisky et al., 1986a, 1986b; Talving, Hayman, & Macdonald, 1991). For example, even after learning has occurred, the knowledge should be relatively inflexible, that is, accessible only when exactly the same cues are presented that were used during training. In addition, the confidence ratings assigned by the patients to their correct choices should be rather low. The patients would have learned to produce a response, not to retrieve items from memory. By contrast, normal subjects should learn quickly and assign confidence ratings appropriate to their level of performance, because they can apply an entirely different strategy to the learning of new associations. They can quickly memorize. The hippocampal formation is specialized for forming conjunctions between arbitrarily different elements, and it is especially good at rapid learning. The literature of classical conditioning makes a similar point. Simple classical conditioning also involves the acquisition of new associations. However, the learning is independent of the hippocampus and typically occurs gradually over many trials. Acquiring associations gradually through classical conditioning is not the same as establishing an association in one trial with the help of the hippocampus. (One example that may blur this distinction is taste-aversion learning, which can occur in one trial and which may not be affected by hippocampal lesions. However, the data on taste-aversion learning and hippocampal lesions are mixed [see Best & Orr, 1973; Murphy & Brown, 1974; Nonneman & Curtis, 1978].)

Multiple Memory Systems: A Biological Perspective

The view advanced here and elsewhere (Squire, 1987) propounds the biological reality of multiple memory systems. Different memory systems are anatomically distinct, and they are involved in acquiring and storing fundamentally different kinds of information. This biological perspective gains support from studies of the amplitude and distribution of event-related potentials (ERPs) elicited during the study of words (Paller, 1990). The ERPs to words that were subsequently recalled were more positive than ERPs to unrecalled words, and this difference was most evident at anterior electrode placements. In contrast, the ERPs to words that were subsequently primed were not measurably different in amplitude from the ERPs to unprimed words. Moreover, the numerical (nonsignificant) differences in amplitude that did occur in the ERPs to primed and unprimed words were greater at posterior electrode placements. Thus, processes related to subsequent declarative memory were electrophysiologically distinct at the time of encoding from processes related to subsequent priming. These results seem easiest to understand in terms of distinct brain systems related to different forms of memory.

Recent findings using PET make this same point (Squire et al., in press). As mentioned earlier, when word stems were presented with instructions to form the first word to come to mind (i.e., priming instructions), there was reduction in blood flow in right extrastriate cortex compared with the baseline condition. By contrast, in a condition that was identical except that subjects were instructed to complete word stems with study words (i.e., memory instructions), there was an increase in blood flow in the right hippocampal region compared with both the priming and the baseline conditions. Thus, brain systems related to declarative memory could be distinguished anatomically from brain systems related to priming. In amnesia, there is an impairment in the ability to acquire and store one kind of memory, which depends on the integrity of the hippocampal region, but other brain systems can support other forms of learning and memory.

As suggested earlier, there is an alternative view as to why amnesic patients exhibit intact learning and memory on many tasks. By this view, the fundamental deficit in amnesia is one of gaining conscious access to an otherwise intact memory store. This idea merits additional discussion. Is it possible that amnesic patients have all of the same information in storage that normal subjects have, and their deficit is that they simply have no conscious access to it? Can all of the information available to normal subjects in principle be expressed by amnesic patients, except that special testing procedures must be used to access the information implicitly?

These questions can be usefully addressed by considering an example from the neuropsychology of vision. The clinical syndrome known as blindsight is characterized by patients who have dramatic loss of visual function but who are capable, given appropriate testing procedures, of a surprising degree of residual vision (Weiskrantz, 1986). The syndrome is caused by a lesion in the visual cortex, which produces a scotoma (area of blindness) in a part of the visual field corresponding to the location of the lesion. Within the scotoma, patients are experientially blind; that is, they deny visual experience. Yet with careful testing, based, for example, on forced-choice procedures, patients are found to be capable of several surprising things. They are able to detect gratings and movement, and they can make accurate reaching movements to objects presented in the blind field. These visual abilities occur without conscious awareness; that is, the patients demonstrate these abilities while reporting the absence of visual experience.

The residual visual abilities of the blindsight patient can be thought of as analogous to the residual memory abilities of the amnesic patient. Both the visual abilities and the memory abilities are available in the absence of awareness that knowledge is being expressed. In the case of amnesic patients, the question is whether they might prove to have as much knowledge available as normal subjects and that it could all be accessed, albeit nonconsciously, if the appropriate tests could be found. In precisely the same sense, the question of interest for the blindsight patient is whether all visual functions might turn out to be available within the blind field. In other words, has only subjective

visual experience been affected by the lesion? Could any visual function in the impaired field be demonstrated if appropriate testing techniques were used?

The answer is clearly no. Some visual function has been lost, for example, the ability to discriminate patterns. Indeed, a double dissociation can be demonstrated: one well-studied patient detected gratings in his intact visual field more poorly than in his impaired visual field (because testing in the normal field was conducted at a very peripheral location). At that same peripheral location in the intact visual field, a triangle and an *X* were discriminated with 90% accuracy using forced-choice testing. However, the triangle versus the X discrimination could not be made at all in the impaired visual field; that is, performance was at chance even with forced-choice testing (Weiskrantz, 1986). Thus, the visual deficit in blindsight is not a selective loss of the experiential component of vision. Pattern vision depends on the integrity of visual cortex and on the projections to visual cortex from the lateral geniculate, and pattern vision is specifically impaired following visual cortical damage (i.e., pattern and form discriminations that cannot be reduced to some simpler kind of discrimination). The residual abilities in blindsight are thought to depend on nonstriate visual mechanisms, including the projections from retina to the superior colliculus in the midbrain.

In amnesia, damage has occurred to the hippocampus, or related structures, and the capacity for one kind of neuroplasticity (LTP in hippocampus) and for one kind of memory is lost. The fact that residual learning abilities are accomplished implicitly could be taken to mean that nothing at all has been lost except the ability to engage in conscious remembering. However, by analogy to the loss of form vision in blindsight, it is suggested here that a specific ability has also been lost in amnesia. What has been lost is the ability to store a particular kind of memory, a kind of memory that is flexible and available to conscious recollection.

Sometimes, what becomes available through implicit memory looks similar to what is available through declarative memory. For example, a presented word may be recalled by declarative memory or the same word may be produced in a priming paradigm. Further examination, however, shows that the information available through priming has very different characteristics compared with what is available through recall (e.g., it is sensitive to modality manipulations and to changes in the physical appearance of stimuli). Moreover, in keeping with the idea that some information has actually been lost, there is no evidence that priming can recover all the information available to declarative memory about a word, for example, when and where it was learned (see Schacter, 1990b; Squire, 1987). What have been preserved in amnesia are various, special-purpose, relatively inflexible memory systems that permit one to behave differently as the result of experience, although usually only gradually over many trials. Brain lesions do not produce losses of awareness without also impairing some domain of information processing.

Time-Limited Role of the Hippocampus: Facts of Retrograde Amnesia

In the previous section, the view was developed that the hippocampus and related structures are essential at the time of learning if declarative (conscious) memory is to be established in an enduring and usable form. In this section, evidence is reviewed to show that the hippocampus has only a temporary role in memory storage. The relevant facts come from studies of retrograde amnesia, that is, the impairment of memories that were acquired before hippocampal damage. Historically, the theoretical significance of retrograde amnesia was first appreciated in the context of human memory disorders. In 1881, Theodule Ribot compiled a large number of case reports with the objective of developing principles of normal memory (Ribot, 1881/1882). He noted that recent memory is typically lost more readily than remote memory and formulated a law of regression that in memory "the new perishes before the old" (p. 127). Quantitative studies of retrograde amnesia in humans began only 20 years ago (Sanders & Warrington, 1971). Since that time, a great deal has been learned, despite the fact that the available methods for assessing remote memory objectively in humans are imperfect in a number of ways.

Quantitative Studies of Retrograde Amnesia in Etiologically Distinct Patient Groups

At the outset, it should be recognized that it has rarely been possible to study retrograde amnesia in patients with selective, histologically confirmed damage to the hippocampus. Indeed, it has only recently become possible (with magnetic resonance imaging) to know which patients being studied have damage to the hippocampus. Although the findings from patients with identified hippocampal lesions are the primary focus here, it is also useful to consider findings from other patients as well (e.g., patients with diencephalic lesions and cases where the anatomical basis of the amnesia is uncertain).

The most useful descriptions of retrograde amnesia have been obtained from quantitative studies of groups of similar patients. The best known and most widely studied example of human amnesia is Korsakoff's syndrome (Albert, Butters, & Levin, 1979; Cohen & Squire, 1981; Kopelman, 1989; Meudell, Northern, Snowden, & Neary, 1980; Squire, Haist, & Shimamura, 1989). The memory impairment in these patients is associated with diencephalic lesions, and the hippocampus is generally intact (for discussion, see Squire et al., 1990). Unfortunately, this group is not advantageous for studies of retrograde amnesia because the amnesic condition often develops gradually over many years. Accordingly, it is difficult to distinguish retrograde and anterograde amnesia unambiguously. Nevertheless, there is general agreement that remote memory impairment in this group is extensive and temporally graded, affecting the recent past more than the remote past (Figure 8, top panel). The remote-memory impairment most likely reflects true retrograde amnesia, not gradually developing anterograde amnesia. In one notable single-case study (Butters & Cermak, 1986), a patient with Korsakoff's syndrome was observed to have forgotten information that he had written in his autobiography a few years before the onset of his amnesia. Extensive retrograde amnesia has also been observed in a severely amnesic patient with Korsakoff's syndrome (patient KJ, Squire, Haist, & Shimamura, 1989) whose family members had witnessed the onset of his amnesia approximately 1 year earlier and could attest to his normal cognitive status before that time.

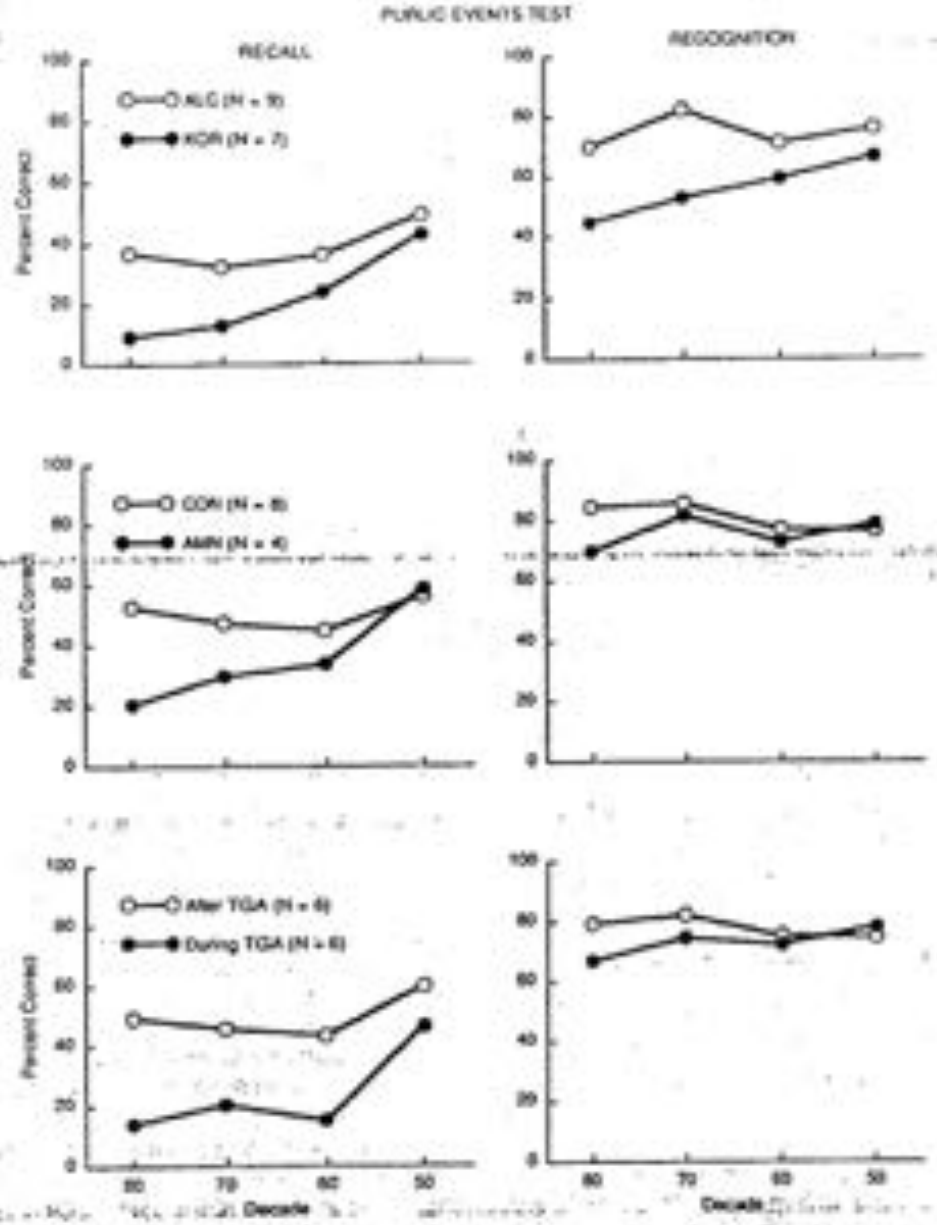

Figure 8. Remote-memory performance of patients with Korsakoff's syndrome (KOR, $n = 7$), alcoholic control subjects (ALC, $n = 9$), amnesic patients with confirmed or suspected damage to the hippocampal formation (AMN, $n = 4$), healthy control subjects (COM, $n = 8$), and patients tested during and after an episode of transient global amnesia (TGA, $n = 6$). Recall: Recall of past public events that had occurred from 1950 to 1985. Recognition: Performance on a multiple-choice test (four alternatives) involving the same public events. (Top four panels from "The Neurology of Memory: Quantitative Assessment of Retrograde Amnesia in Two Groups of Amnesic Patients" by L. R. Squire, F. Haist, and A. P. Shimamura, 1989, *Journal of Neuroscience, 9*, p. 830–831. Copyright 1989 by Oxford University Press. Reprinted by permission. Bottom two panels from "Transient Global Amnesia: Evidence for Extensive, Temporally-Graded Retrograde Amnesia" by M. Kritchevsky and L. R. Squire, 1989, *Neurology 39*, p. 215. Copyright 1989 by Edgell Communications. Adapted by permission.)

More favorable circumstances for the study of retrograde amnesia occur with patients who became amnesic suddenly on a known calendar day. In this case, there can be no ambiguity about which test items measure retrograde amnesia. Tests of remote memory have now been given to two groups of such patients. One group ($n = 4$) had presumed or confirmed damage to the hippocampal formation (patients AB, GD, WH, and LM from Squire, Haist, & Shimamura, 1989). They exhibited extensive and temporally graded retrograde amnesia, covering on average about 15 years of the period before the onset of amnesia

(Figure 8, middle panel). In separate tests, very remote memory was intact even when the test items were so difficult that they could be answered by fewer than 20% of normal subjects (Squire, Haist, & Shimamura, 1989).

Another group of six patients was studied during and after transient global amnesia (TGA), a neurological syndrome characterized by the sudden onset of severe and selective amnesia that typically lasts 6 to 10 hr. These patients also exhibited extensive, temporally graded retrograde amnesia (Figure 8, bottom panel; Kritchevsky & Squire, 1989; Kritchevsky, Squire, & Zouzounis, 1988). One methodological advantage of this group is that the patients serve as their own control subjects. Thus, the patients were tested while they were amnesic, and at that time they failed questions about public events that they could later answer correctly after recovery from TGA. In addition, as judged by less formal questioning carried out after recovery, permanent memory loss often occurred for information that had been acquired from a few hours to 1 to 2 days before the episode. Also, memory for the events that had occurred during the period of anterograde amnesia was permanently lost.

The results from these three patient groups (patients with Korsakoff's syndrome, the 4 patients with confirmed or suspected hippocampal damage, and TGA patients) show clearly that retrograde amnesia can be extensive and temporally graded. Indeed, all three groups of amnesic patients had similarly extensive and temporally graded retrograde amnesia as measured by the same recall tests of remote memory. Temporally graded remote memory impairment was also detectable, but less severe, when memory was assessed by multiple-choice and yes–no recognition.

Retrograde Amnesia in Patients With Hippocampal Lesions

Retrograde amnesia can be less extensive than in the patients just described. Consider, for example, patient R. B. who had moderately severe anterograde amnesia in association with ischemic damage that was limited to the CA1 region of the hippocampus bilaterally (Zola-Morgan et al., 1986). For this patient, retrograde amnesia could not be detected in any of six different tests, including the same remote-memory test that was given to the three groups of patients discussed earlier (cf. Figure 8 and top two panels of Figure 9). It is possible that R. B. had some retrograde amnesia for a period of a few years or less before the onset of his amnesia in 1978 (Figure 9; detailed recall of public events and the television test). However, the available tests cannot detect such a deficit reliably in a single subject.

Retrograde amnesia appears to vary in its severity and extent as a function of the severity of anterograde amnesia, at least across a considerable range of severity. (For evidence that retrograde and anterograde amnesia can nevertheless be dissociated, see the following section.) Retrograde amnesia is brief when anterograde amnesia is only moderately severe (e.g., patient R. B.). It is more extensive when anterograde amnesia is more severe than in patient R. B., as was the case for the patient groups considered earlier (the patients with Korsakoff's syndrome, the 4 amnesic patients with confirmed or suspected hippocampal pathology, and the 6 patients with TGA). For example, the group of 4 patients with hippocampal lesions had more severe anterograde amnesia than did R. B. (the IQ–memory quotient [MQ] difference score for the 4 patients = 29.0 vs. 20 for R. B.) and also had more severe retrograde amnesia (compare Figure 8, middle panels, and Figure 9, top panel). Correspondingly, these 4 patients probably had more extensive neuropathology than was found in R. B. Indeed, 2 of the patients in this group have been examined with an improved protocol for imaging the human hippocampus with magnetic resonance (patients L. M. and W. H., Press et al., 1989; Squire et al., 1990). Whereas R. B. had damage limited to the CA1 field of hippocampus, in both L. M. and W. H. the hippocampal formation was markedly reduced in size bilaterally, affecting all the cell fields of the hippocampus, including the CA1 field, together with the dentate gyrus and the subicular complex. These findings suggest that pathology in the hippocampal region, if it involves more than just the CA1 field, can produce relatively severe anterograde and retrograde amnesia. Thus, one can tentatively identify two levels of memory impairment from the human cases: a moderately severe anterograde amnesia and limited retrograde amnesia associated with damage limited to the CA1 field of hippocampus and more severe anterograde and retrograde amnesia associated with more extensive damage to the hippocampal region.

This proposed link between the severity of anterograde and retrograde amnesia would appear to be contradicted by findings from the well-studied patient H. M., who at the age of 27 (in 1953) sustained bilateral removal of the medial temporal lobe for the relief of severe epilepsy. The surgical lesion was intended to include the hippocampal formation, the amygdala, and underlying cortex. Following the surgery, H. M. developed a more severe anterograde amnesia than is observed in any of the patients discussed thus far. The extent of his retrograde amnesia is more difficult to judge, in part because quantitative assessments were not undertaken until more than 20 years after he became amnesic. Nevertheless, he is reported to have retrograde amnesia for a period covering only 3 to 11 years before his surgery (Corkin, 1984; Marslen-Wilson & Teuber, 1975; Milner et al., 1968; Sagar, Cohen, Sullivan, Corkin, & Growdon, 1985; Scoville & Milner, 1957). It is possible that very early memories are especially resistant to amnesia. If H. M. had developed amnesia in middle age, like the majority of amnesic study patients, perhaps he would have exhibited more extensive retrograde amnesia. In any case, more recent findings do support the idea that anterograde amnesia and temporally graded retrograde amnesia are related deficits.

Retrograde Amnesia Without a Temporal Gradient

It is important to note that some memory-impaired patients have extensive retrograde amnesia with no evidence of a temporal gradient. In such cases, remote memory appears to be severely and similarly impaired across all time periods (for example, following left unilateral temporal lobectomy and in association with some cases of diencephalic amnesia, Huntington's disease, Alzheimer's disease, encephalitis, or head trauma; Albert, Butters, & Brandt, 1981; Barr, Goldberg, Wasserstein, & Novelly, 1990; Beatty, Salmon, Butters, Heindel, & Granholm, 1988; Butters & Stuss, 1989; Cermak & O'Connor, 1983; Damasio, Graff-Radford, Eslinger, Damasio, & Kassell, 1985; Graff-

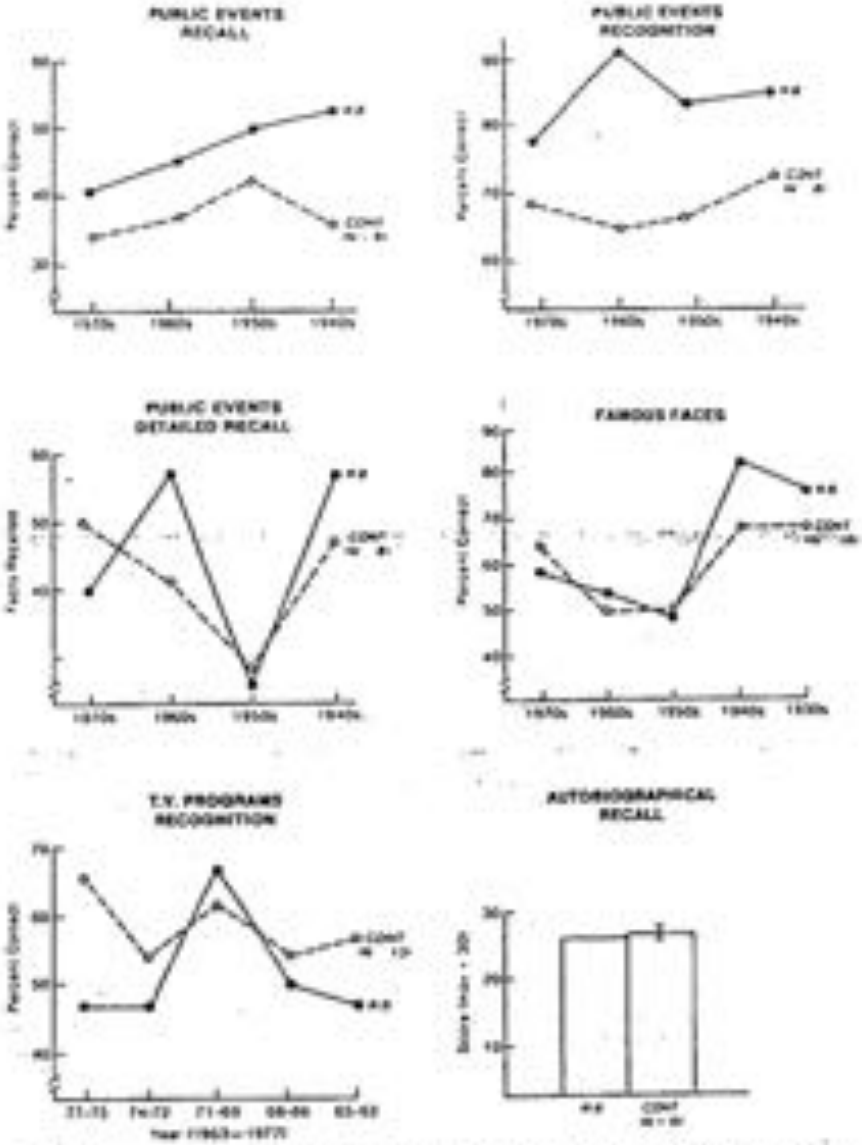

Figure 9. Performance on six tests of remote memory by amnesic patient R. B. (R.B). (The first 5 tests were given in 1979, 7 to 10 months following the onset of his amnesia. Recall of personal episodes was tested 2 years after the onset of his amnesia. CONT = control subjects. From "Human Amnesia and the Medial Temporal Region: Enduring Memory Impairment Following a Bilateral Lesion Limited to Field CA1 of the Hippocampus" by S. Zola-Morgan, L. R. Squire, and D. G. Amaral, 1986, *Journal of Neuroscience, 6*, p. 2954. Copyright 1986 by Oxford University Press. Reprinted by permission.)

Radford et al., 1990; Sagar et al., 1988; Stuss, Guberman, Nelson, & Larochelle, 1988; Warrington & McCarthy, 1988; Tulving, Schacter, McLachlan, & Moscovitch, 1988; Wilson, Kaszniak, & Fox, 1981; also see one early report involving a mixed group of amnesic patients, Sanders & Warrington, 1971). This type of retrograde amnesia deserves special consideration. One possibility is that ungraded retrograde amnesia is simply the extreme on a continuum of severity. By this view, the same patients have both very severe anterograde amnesia (i.e., more severe than any of the patients represented in Figure 8) and correspondingly severe retrograde amnesia. The difficulty with this view is that not all the patients with extensive and severe retrograde amnesia appear to have severe anterograde amnesia. Perhaps the clearest example of such a dissociation is found in the patients with left temporal lobectomy studied by Barr et al. (1990). The patients were only mildly impaired on tests of delayed story recall (not nearly so impaired as the patients whose remote memory scores are shown in Figure 8), but these patients had extensive and ungraded retrograde amnesia on several remote memory tests that assessed knowledge of famous persons, public events, and television programs.

Another possibility is that severe and ungraded retrograde amnesia requires damage in addition to (or different from) the medial temporal lobe and midline diencephalic structures

usually associated with circumscribed amnesia. This alternative seems plausible because most, if not all, of the clinical conditions in which ungraded retrograde amnesia has been reported are conditions in which additional damage is known to have occurred (e.g., to lateral temporal cortex). This additional damage might impair performance on remote-memory tests without contributing proportionally to anterograde amnesia. For example, memory storage sites or access to them could be compromised by lateral temporal cortex lesions, without destroying the capacity to establish new representations that are based on different cues and processing strategies and that are therefore stored in a different area of cortex. Additional neuropsychological and anatomical information will be needed to identify the determinants of ungraded retrograde amnesia and to confirm that ungraded forms of retrograde amnesia are dissociable from anterograde memory impairment.

Retrograde Amnesia for Autobiographical Memory

Most quantitative assessments of retrograde amnesia have been based on tests of public information (e.g., tests of public events and famous faces), because the correct answers can be identified unambiguously. However, tests have also been constructed to assess autobiographical, event-specific memory (e.g., subjects are asked to recollect personal episodes in response to a fixed list of cue words [Crovitz & Schiffman, 1974; Galton, 1879] or to recollect specific episodes in response to structured questions). Frank confabulation is ruled out by determining that subjects are consistent about the telling of the event and its date on two different occasions several weeks apart. On such tests, amnesic patients typically exhibit temporally limited retrograde amnesia (Figure 10). For example, 2 patients with confirmed hippocampal damage (patients L. M. and W. H.), who were normal on tests of factual information for very remote events (Figure 8), were also able to produce well-formed memories from their early childhood or adolescence

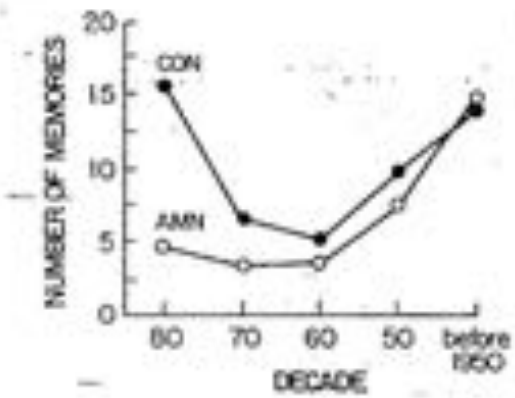

Figure 10. Time periods (before 1950 through 1980) from which 5 amnesic patients (AMN) and 5 control subjects (CON) recalled well-formed autobiographical memories in response to 75 single-word cues (e.g., tree, flag, or window). From "Autobiographical Memory in Amnesia" by D. MacKinnon and L. R. Squire, 1989, *Psychobiology 17*, p. 250. Copyright 1989 by the Psychonomic Society, Inc. Reprinted by permission.

(MacKinnon & Squire, 1989). The quality of their memories could not be differentiated from those reported by normal subjects. Moreover, just as was observed in the case of factual information tests, they were impaired when they attempted to recollect more recent events. Altogether, 5 amnesic patients took both tests, and they had similarly severe autobiographical memory impairment and fact-memory impairment.

It has often been reported that memory impairment for factual information and memory impairment for autobiographical material are associated in individual patients (Beatty, Salmon, Bernstein, & Butters, 1987; Butters & Cermak, 1986; Gabrieli, Cohen, & Corkin, 1988; Kopelman, 1989; Ostergaard, 1987). The same patients who exhibit extensive ungraded retrograde amnesia for factual information are also often reported to be unable to produce any autobiographical memories at all (Cermak & O'Connor, 1983; Damasio et al., 1985; Tulving et al., 1988; Warrington & McCarthy, 1988). In general, the findings for autobiographical tests and fact memory tests appear to be in correspondence. Those patients who cannot recollect personal memories also exhibit extensive, ungraded remote-memory impairment, whereas those who can recall early personal memories exhibit temporally graded retrograde amnesia for factual information with sparing of very remote memory.

One difficulty in comparing fact memory with autobiographical memory for personal events is that factual knowledge can be acquired through repeated exposure to information. By contrast, remembered events are specific to time and place and cannot be repeated. When amnesia occurs, so long as it is not so severe as to be absolute, one would expect material that has been often repeated to be easier to remember than material that has occurred only once (see Ostergaard & Squire, 1990). This simple difference between facts and events is one reason why event memory can appear to be more affected in amnesia than fact memory. On the one hand, it is clear that both fact memory and event memory are impaired in amnesia, especially if the information was acquired recently. On the other hand, severely amnesic patients have been described who reportedly have some remote fact memory available but no capacity at all for autobiographical, event-specific recall (e.g., Damasio et al., 1985; Tulving et al., 1991; Tulving et al., 1988). This finding has sometimes been taken to suggest that amnesia especially affects episodic memory. However, the issue is not that such patients can accumulate some semantic (factual) knowledge without acquiring episodic (event) knowledge. The issue is whether the ability to acquire factual knowledge is disproportionately spared. Is the ability to accumulate factual information better than would be expected, given the level of memory ability for unique events? Further study is needed of this interesting issue.

Retrograde Amnesia as a Stable Impairment

Everyone has the experience of failing to recollect a piece of information that could be recalled successfully on some later occasion. Following from this observation, it seems possible that amnesic patients (as well as normal subjects) know more about remote events than they are able to demonstrate in one test session. In the limiting case, if a sufficient number of testing occasions were provided, one could suppose that amnesic

patients might eventually produce as much information about remote events as normal subjects (Cermak & O'Connor, 1983). This possibility has been tested by administering the same remote memory tests on multiple occasions during a 3-year period to normal subjects and amnesic patients (Squire, Haist, & Shimamura, 1989). On each test occasion, it was found that information could usually be recalled that had not been recalled on previous tests. However, the amount of new information that amnesic patients could add at each test session eventually became quite small, and their cumulative performance score leveled off to an asymptote well before the amount that they could recall reached normal levels. This result indicates that retrograde amnesia is not a problem in assessing memory that can be overcome with sufficient retrieval opportunity. On the contrary, it appears that amnesic patients simply possess less usable knowledge about past events than normal subjects, and their retrograde amnesia is a stable feature of their memory impairment.

Recently, this view was questioned by a report that retrograde amnesia could be attenuated by altering the manner in which remote memory questions are presented. Specifically, findings from a single case of postencephalitic amnesia suggested that retrograde amnesia was severe and extensive when assessed with standard tests but that it was not observed at all when remote-memory tests were redesigned as semantic-memory tests (Warrington & McCarthy, 1988). The new remote-memory tests assessed simple familiarity for famous names or name-completion ability rather than associative memory. However, one possibility is that such tests were simply too easy to detect a difference between normal and abnormal performance; that is, impaired performance might have been obscured by a ceiling effect.

To explore this issue, my colleagues and I constructed similar tests but made them difficult enough that subjects did not achieve perfect performance (Squire, Zola-Morgan, Cave, Haist, Musen, & Suzuki, 1990). Two amnesic patients were tested with radiologically confirmed lesions that included the hippocampus bilaterally—patient Boswell (Damasio et al., 1985) and patient W. J. (Squire, Amaral, & Press, 1990). Both patients had severe and extensive retrograde amnesia as assessed by standard recognition tests of remote memory; that is, they performed more poorly than the patients whose data appear in Figure 8. (Note that the standard tests of remote memory are sometimes not very sensitive to retrograde amnesia when they are given in a recognition format [see Figure 8, right panels]. Accordingly, only severely impaired patients have room to improve on such tests, and only these patients can provide a test of the idea that performance will improve when the nature of the remote-memory test is altered.) In the first test (familiarity) subjects were asked to select the famous name from a group of nonfamous names (e.g., Arthur Elliot, David Conner, or *Richard Daly*). The second test asked subjects to complete a fragment to form a famous name (e.g., Adlai Stev—). The correct answers for both tests were taken from a standard test of remote memory for famous faces and spanned the time period 1940–1985.

On the redesigned tests, the amnesic patients did perform better than on more conventionally designed tests (e.g., select from a group of famous names the one that matches a photograph). However, the normal subjects also performed better on the redesigned tests, and they retained their substantial advantage over the amnesic patients. Indeed, both amnesic patients scored outside the range of the scores obtained by normal subjects, and they were more than two standard deviations below the normal mean. These findings provide no basis for supposing that retrograde amnesia can be mitigated by simple changes in test procedure. Retrograde amnesia reflects a stable impairment in accessing past facts and events.

Temporally Graded Retrograde Amnesia

The data just reviewed show that retrograde amnesia is a typical feature of memory impairment. In most cases, and certainly when damage is limited to the hippocampal formation, retrograde amnesia is temporally graded such that recent memory is more impaired than remote memory. Its severity and extent are related to the severity of anterograde amnesia and determined by the extent of damage within the medial temporal lobe and midline diencephalon. When damage is more extensive and includes, for example, lateral temporal neocortex, remote-memory impairment can be severe and ungraded, perhaps because there is direct damage to memory storage sites. In these cases, the link between anterograde and retrograde amnesia is less clear.

Because very remote memories are typically preserved in amnesic patients, including those with substantial hippocampal damage, the site of permanent memory storage cannot be the hippocampus itself or any of the damaged structures. For this reason, it has long been supposed that the hippocampus (and related structures) must have only a temporary role in memory storage. There are two fundamentally different ways to understand this idea. One possibility is that the structures damaged in amnesia are necessary for the storage and retrieval of memory, but especially the storage and retrieval of those components of memory that tend to be forgotten quickly. A complete memory for any single event (e.g., dinner with a friend) is assumed to consist of many component memories, which have different qualities and varying lifetimes. Details, context, and other incidental features (e.g., what the friend was wearing) will on average be forgotten quickly after learning and will be rare in very long-term memory. The more generic and central features of the event (e.g., that dinner with a friend did take place) will be remembered longer. If the structures damaged in amnesia are necessary for storing and retrieving context and detail, that is, the short-lasting components of memory, then it follows that amnesia will always appear to affect recent memory more than remote memory. Temporally graded retrograde amnesia occurs simply because these components are more abundant in recent memory than in remote memory. There is no transformation or consolidation of information across time. There is simply differential attrition of memory by type. The structures damaged in amnesia have a temporary role in memory because the kind of memory served by these structures is present only temporarily.

A second possibility is that the structures damaged in amnesia have a temporary role in the sense that memories that initially depend on these structures become independent as time

passes. That is, memories are reorganized or consolidated with the passage of time after learning.

These two possibilities can be distinguished experimentally by determining the precise shape of the performance curves in retrograde amnesia. Consider the two sets of hypothetical data shown in Figure 11. In Alternative A, the score for any particular time period is never lower than the score for a more remote time period. These data can be explained by supposing that memories for the very remote past that have survived for many years never depended on the structures damaged in amnesia, even when they were first acquired. Only the more quickly forgotten memories depend on these structures. In this view, the ability to recall the recent past can never be poorer than the ability to recall the remote past. In Alternative B, scores for recent time periods are actually lower than scores for more remote time periods. These data cannot be accounted for by supposing that amnesia especially impairs rapidly decaying memories. One must explain why in amnesia, older memories could be remembered better than recent memories.

It has been difficult to decide between these two alternatives. The difficulty is that the precise shape of the temporal gradient of retrograde amnesia cannot be determined with certainty using the tests that are available to assess remote memory retrospectively in humans. Nevertheless, gradients of retrograde amnesia have been obtained in which the remote past was remembered better than the recent past. In one instance, psychiatric patients prescribed electroconvulsive therapy (ECT) were tested both before and after treatment using a test that was specially constructed to permit equivalent sampling of past time periods (Squire, Slater, & Chace, 1975). After treatment, the patients had difficulty remembering events that had occurred 1 to 3 years earlier, whereas more remote events were remembered normally. In a second instance, mice were trained in a one-trial learning task and then given electroconvulsive shock (ECS) at different times after learning (Squire & Spanis, 1984). Memory for the training was impaired when the training occurred 1 to 3 weeks before ECS but not when it occurred at earlier times. These findings show (in agreement with Alternative B) that

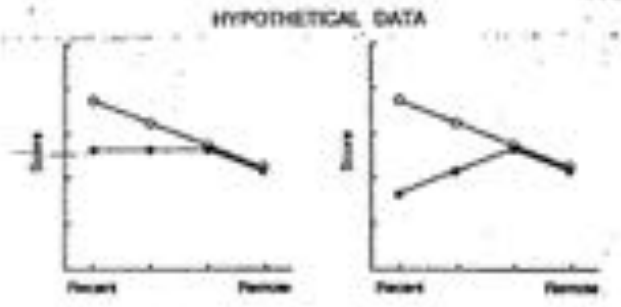

Figure 11. Hypothetical data (A and B) derived from an optimal remote-memory test that can sample equivalently across time periods; that is, the material from each time period was initially learned to the same level and then forgotten at the same rate. (Only the data in the right panel require that memory is actively reorganized or consolidated as time passes after learning. The key feature of these data is that memory for remote time periods is better than memory for more recent periods. Open circles = normal subjects; closed circles = amnesic patients.)

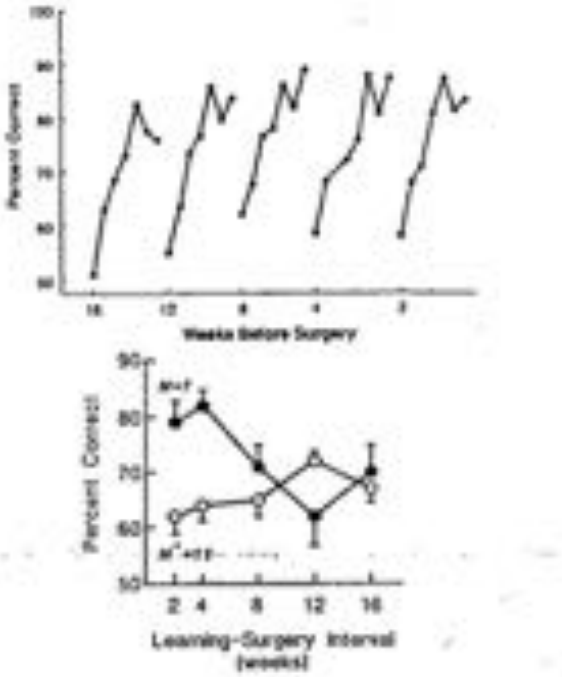

Figure 12. Top: Acquisition of 100 object-discrimination problems (20 pairs/time period) before surgery. (Bottom: Retention of the 100 object pairs as a function of learning–surgery interval. Monkeys with bilateral lesions of the hippocampal formation and parahippocampal gyrus [H] exhibited temporally graded retrograde amnesia. Normal monkeys [N] exhibited forgetting. From "The Primate Hippocampal Formation: Evidence for a Time-Limited Role in Memory Storage" by S. Zola-Morgan and L. R. Squire, 1990, *Science, 250*, p. 289. Copyright 1990 by the American Association for the Advancement of Science. Reprinted by permission.)

long-term memory is dynamic and that memory must change as time passes after learning. However, treatments like ECT and ECS cannot be usefully related to neuroanatomy or to hippocampal function.

Recently, a direct test of Alternatives A and B was arranged by studying memory prospectively in monkeys with bilateral lesions of the hippocampal formation (the H lesion; Zola-Morgan & Squire, 1990c). Monkeys were trained preoperatively on five different sets of 20 object-discrimination pairs (for a total of 100 object pairs). Training on each 20-pair set began approximately 16, 12, 8, 4, and 2 weeks before surgery. For training, each object pair was presented for 14 trials, and during training performance improved from 55% correct on the 1st trial (chance = 50%) to 88% correct on the 14th trial (averaged across all 100 object pairs). One of the two objects was always rewarded, and the left–right location of the correct object varied randomly. The learning curves were numerically quite similar for the five training episodes (Figure 12, top).

Two weeks after surgery, memory was assessed by presenting a single trial for each of the 100 pairs in a mixed order. Figure 12 (bottom) shows the mean retention scores as a function of learning–surgery interval. Unoperated monkeys ($n = 7$) exhibited forgetting, ranging from 79% correct for objects learned recently to less than 70% correct for objects learned in the most

remote time periods. The H⁻ group ($n = 11$) exhibited temporally graded retrograde amnesia. Specifically, the operated monkeys performed more poorly than the normal monkeys on object pairs that had been learned 2 to 4 weeks before surgery ($p < .01$). The two groups did not differ at any other time periods. The key finding was that the operated monkeys remembered objects learned long before surgery significantly better than objects learned recently. In addition, the retrograde amnesia gradient was monotonic from 2 weeks to 12 weeks (62%, 64%, 65%, and 72%), and there was a significant linear trend ($p < .01$) across this portion of the performance curve. Indeed, of the 11 H⁻ monkeys, only 1 remembered the objects learned 2 weeks before surgery better than the objects learned 12 weeks before surgery. For the 7 normal monkeys, the opposite was true: Only 1 monkey remembered the 12-week old objects better than the 2-week old objects.

One would expect that, if all relevant time periods had been fully sampled, the performance curve of operated animals should approximate an inverted *U*. In other words, if the memory scores of operated monkeys do increase significantly as one moves from a recent to a more remote time period, at some point in very remote time periods the scores of operated monkeys would be expected to join the forgetting curve of normal monkeys.

These results provide evidence for a gradual process of consolidation or reorganization in memory as time passes after learning. Similar results were also reported recently for rats given hippocampal lesions, although in this case (Winocur, 1990) the gradient of retrograde amnesia extended across a period of only 2 to 5 days (also see Cho, Beracochea, & Jaffard, 1991; Sutherland, Arnold, & Rodriguez, 1987, for two preliminary reports). Thus, the hippocampal formation is essential for memory storage for only a limited period of time. A temporary memory is established in the hippocampal formation at the time of learning (in the form of a simple memory, a conjunction, or an index; Halgren, 1984; Marr, 1971; McNaughton & Nadel, 1990; Milner, 1989; Rolls, 1990; Squire, Shimamura, & Amaral, 1989; Teyler & Discenna, 1986). The role of the hippocampus then gradually diminishes, and a more permanent memory is established elsewhere that is independent of the hippocampus.

These ideas about the significance of retrograde amnesia and the reorganization of memory over time are ideas specifically about declarative memory. Hippocampal lesions in monkeys did not affect previously learned motor skills (Salmon et al., 1987). In addition, patients who were amnesic following a prescribed course of ECT retained a mirror-reading skill that they had acquired before treatment, despite forgetting the words they had been read and even the training sessions themselves (Squire, Cohen, & Zouzounis, 1984).

Retrograde Amnesia: A Summary

The facts of retrograde amnesia, as they are now understood, require a gradual process of reorganization or consolidation within declarative memory, whereby the contribution of the hippocampus and related structures gradually diminishes and the neocortex alone gradually becomes capable of supporting usable, permanent memory. This reorganization could depend on the development of effective cortico-cortical connections between the separate sites in neocortex, which together constitute the whole memory, or it could require the development of new representations. In either case, it would seem that slow changes in synaptic connectivity must be involved. One possibility is that consolidation is a part of the biologic process of forgetting and that the connections between some elements of representations are lost over time, whereas other connections grow stronger (Squire, 1987).

Temporally graded retrograde amnesia (as in Alternative B, Figure 1) has now been observed in mice, rats, monkeys, and humans. The length of the retrograde amnesic gradient was short in mice (1–3 weeks), intermediate in monkeys (2–12 weeks), and longer in humans (1–3 years). The length of the gradient can be expected to vary depending on the extent of damage to the medial temporal lobe memory system and on the course of normal forgetting for the material being tested. It is also likely that more recently evolved, more complex vertebrates have more slowly developing memory consolidation processes than simpler vertebrates. Indeed, the time required for neuroplasticity to develop may generally be slower in more complex nervous systems. For example, an independent, secondary epileptic focus (*mirror focus*) in the hemisphere contralateral to the site of an artifically induced primary epileptic lesion develops more slowly in cats and monkeys than in frogs, rats, and rabbits (Wilder, 1972).

More than 100 years have passed since Theodule Ribot first pointed out the lawfulness of memory loss for past events and the relative preservation of remote memory. Prospective studies involving experimental animals show how this observation should be interpreted. Sparing of remote memory in amnesia is not based on the greater rehearsal and repetition of remote events compared with recent events, because sparing of remote memory can occur in amnesia even when the remote material is remembered less well by normal subjects than recently learned material. In addition, sparing of remote memory does not reflect the survival of particular components of memory that did not depend at any time after learning on the structures damaged in amnesia. Rather, the phenomenon results from the fact that the damaged structures have only a temporary role in memory.

The concept of consolidation was originally advanced to explain retroactive interference (Muller & Pilzecker, 1900) but found its strongest support in the phenomenon of retrograde amnesia (Burnham, 1903). Subsequently a large body of experimental work illustrated convincingly the utility of the concept of consolidation for understanding the phenomenon of retrograde amnesia (McGaugh & Gold, 1976; McGaugh & Herz, 1972). More recent work with experimental animals shows that consolidation can continue for a long period and suggests how the hippocampal formation is involved in the process. The hippocampus must initially participate in establishing representations, if memory is to be established in a usable way. Gradual reorganization of memory storage occurs such that storage and retrieval is eventually possible without the participation of the hippocampus or related structures.

The facts of retrograde amnesia can be summarized as follows:

1. When damage is limited to the CA1 region of human

hippocampus, retrograde amnesia is limited to a period of a year or 2 at the most.

2. In patients with more complete damage to the hippocampal formation, retrograde amnesia can be extensive and temporally graded across a decade or more, with sparing of very old memories.

3. Hippocampal damage causes retrograde amnesia for both factual information and autobiographical, event-specific information.

4. The retrograde amnesia represents a loss of usable knowledge, not a loss of accessibility that can be overcome by multiple retrieval opportunities.

5. Retrograde amnesia is a retrieval deficit in the sense that lost memories return following transient amnesic episodes. However, memory for the time period just before the onset of amnesia is permanently lost. Moreover, it cannot be assumed that past memories would recover to the same extent if the period of amnesia lasted longer than it typically does in transient amnesia. Some clinical observations on this point (see Squire, Cohen, & Nadel, 1984) raise the possibility that memory becomes progressively disorganized so long as the hippocampal system remains dysfunctional. Thus, when the system regains its normal function quickly as in transient global amnesia, past memories are once again available. However, if the system were to remain dysfunctional for many weeks or longer, memory might not recover so fully. These considerations suggest that, rather than describing retrograde amnesia as a retrieval deficit, it is more accurate to describe it as a loss of access, the nature of which is determined by the status of memory in storage when amnesia occurs.

6. Retrograde amnesia is revealed in tests that require associative memory as well as in tests that require simple recognition on the basis of familiarity. To date, there have been no convincing demonstrations that retrograde amnesia can be mitigated by changing test procedures (except in the theoretically uninteresting case where two different tests have similar effects on both normal subjects and amnesic patients, e.g., administering a test of recognition memory instead of a test of recall).

7. Work with experimental animals provides direct evidence for gradual consolidation of memory during the period of normal forgetting and for the involvement of the hippocampus in this process. The hippocampus is required initially for the storage and retrieval of memory, but not after sufficient time has passed.

Conclusion

Coordinated neural activity in neocortex is thought to underlie perception and the capacity for immediate (short-term) memory (Damasio, 1989; Mishkin, 1982; Squire, 1987; also see Singer, 1990). Consider for example the problem of remembering a single visual object (Figure 13). Activity in the inferotemporal cortex (area TE) is believed to be important for processing information about the quality of the object, and activity in parietal cortex (area PG) is believed to be important for processing information about the location of the object in space and its relationship to other objects (Ungerleider & Mishkin, 1982). If this neural activity is to cohere into a stable declarative memory,

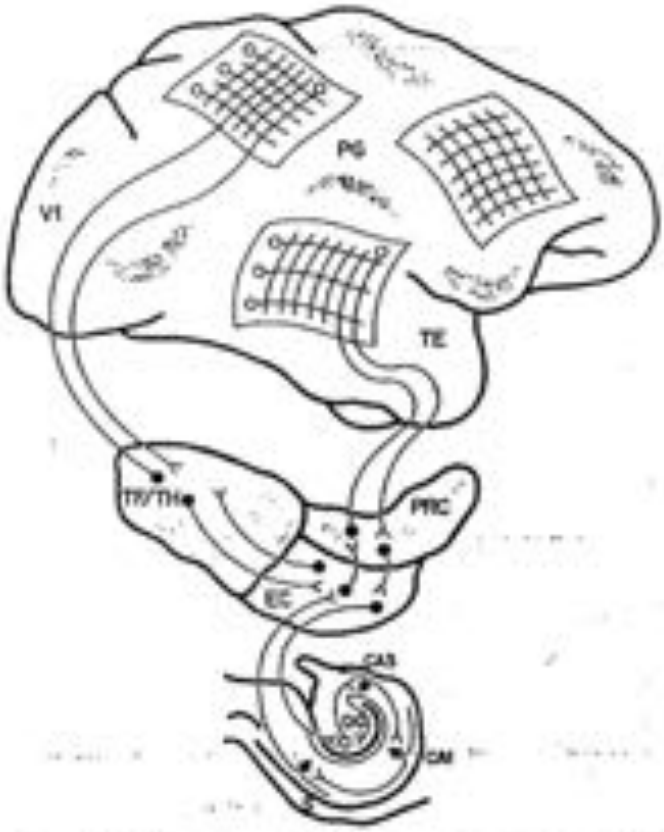

Figure 13. Schematic drawing of primate neocortex together with the structures and connections in the medial temporal lobe memory system believed to be important for establishing long-term memory (see text). (PG = parietal cortex; TE = inferotemporal cortex; TF/TH = parahippocampal cortex; PRC = perirhinal cortex; EC = entorhinal cortex; DG = dentate gyrus; S = subiculum; CA1 and CA3 are fields of the hippocampus. From "Closing Remarks," p. 648, by L. R. Squire, 1990, in L. R. Squire and E. Lindenlaub, *The Biology of Memory*, Stuggart, Federal Republic of Germany: F. K. Schattauer Verlag. Copyright 1990 by F. K. Schattauer Verlag. Adapted by permission.)

then convergent activity must occur within anatomical projections from these regions into the medial temporal lobe memory system. Projections from the medial temporal lobe to medial thalamic structures important for forming declarative memory are not illustrated in the Figure. In addition, projections from both the medial temporal lobe and the diencephalon to the frontal lobe are presumed to be important for translating memory into action.

Other effects of having perceived the visual object can persist in forms of nonconscious memory that do not require the participation of this system. First, the facility for subsequently perceiving and detecting the same object will increase, and preferences and other judgments involving this and similar objects can be influenced. These products of experience depend especially on changes in early-stage processing systems in posterior neocortex. It is not necessary that a preexisting representation of the percept be available for activation. In addition, visual objects could serve as conditioned stimuli (CS) in classical conditioning paradigms, wherein objects could acquire either posi-

tive or negative value, and come to elicit any of several responses, depending on the nature of the unconditioned stimulus predicted by the CS. In these cases, the amygdala may be important for associating positive or negative value to the object, and the cerebellum, for developing the conditioned response (when it depends on skeletal musculature).

A visual object could also serve as a discriminative cue in an operant conditioning paradigm, or in any number of win-stay, habit-learning tasks that involve the gradual acquisition of object–reward associations. These cases appear to depend on an interaction between the neocortex and the striatum. Finally, the ability to classify objects can develop after repeated experience with several different objects, at least when classification learning is based on exemplars described by fixed rules. This kind of knowledge can develop independently of declarative memory for individual objects. Although no information is available about the neural basis for classification learning, an interesting possibility is that it too depends on cortico–striatal interaction.

Declarative memory, the ability to remember after a single trial that the visual object was presented and that it occurred in a particular context, requires that an interaction be established at the time of learning between the neocortex and the medial temporal lobe memory system. Figure 13 shows projections from putative networks in neocortex converging on the parahippocampal gyrus (area TF/TH) and perirhinal cortex (PRC). These regions in turn originate projections to entorhinal cortex, the gateway to the hippocampus. Other routes from neocortex to entorhinal cortex may also be important, but fully two-thirds of its cortical input originates in the perirhinal and parahippocampal cortices (Insausti et al., 1987). Further processing of the input occurs in the several subdivisions of the hippocampus, and the fully processed input eventually exits by way of the subiculum and the entorhinal cortex, where widespread efferent projections then return to neocortex.

At the time of learning, neural changes occur at one or more of these stages, possibly as a result of long-term potentiation (LTP). These sites of neuroplasticity act as conjunctions that temporarily bind together the areas in neocortex that originated the convergent input. It is possible that the cortical regions adjacent to the hippocampus (entorhinal cortex, parahippocampal cortex, or perirhinal cortex) are also sites of plasticity and that these sites participate together with the hippocampus in supporting storage sites in neocortex.

In this view, simultaneous and coordinated activity in neocortex is sufficient for the task of perception and short-term memory. So long as a visual object is in view or in mind, its representation remains coherent. However, a distinct problem arises when one's attention shifts to a new scene or a new thought, and one then attempts at a later time to recover the visual object from memory. In the present account, the possibility of later retrieval is provided by the hippocampal system because it has bound together the relevant cortical sites. A partial cue that is later processed through the hippocampus is able to reactivate all of the sites and thereby accomplish retrieval of the whole memory.

This state of affairs is only temporary. As the result of gradual processes that are still poorly understood, the organization of memory storage is slowly transformed as time passes after learning. This transformation could involve rehearsal, additional retrieval opportunities, or acquisition of related material, or it could be largely endogenous. In any case, with time, the role of the hippocampal system diminishes until it is no longer necessary for either the maintenance of memory in storage or its retrieval. Concurrently, the sites of storage in neocortex undergo two related kinds of changes. First, forgetting occurs, probably because of the establishment of new connections, which interfere with the coherence of already established networks, as well as the actual weakening or loss of existing connections within established networks. Second, the distributed networks that together constitute a whole memory develop greater coherence, perhaps by developing functional cortico–cortical connections (as between areas TE and PG) or by representing information in a more efficient form. As a result of these changes, remembering becomes possible without the participation of the medial temporal lobe or the diencephalon.

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