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THE MEDIAL TEMPORAL LOBE

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■ **Abstract** The medial temporal lobe includes a system of anatomically related structures that are essential for declarative memory (conscious memory for facts and events). The system consists of the hippocampal region (CA fields, dentate gyrus, and subicular complex) and the adjacent perirhinal, entorhinal, and parahippocampal cortices. Here, we review findings from humans, monkeys, and rodents that illuminate the function of these structures. Our analysis draws on studies of human memory impairment and animal models of memory impairment, as well as neurophysiological and neuroimaging data, to show that this system (*a*) is principally concerned with memory, (*b*) operates with neocortex to establish and maintain long-term memory, and (*c*) ultimately, through a process of consolidation, becomes independent of long-term memory, though questions remain about the role of perirhinal and parahippocampal cortices in this process and about spatial memory in rodents. Data from neurophysiology, neuroimaging, and neuroanatomy point to a division of labor within the medial temporal lobe. However, the available data do not support simple dichotomies between the functions of the hippocampus and the adjacent medial temporal cortex, such as associative versus nonassociative memory, episodic versus semantic memory, and recollection versus familiarity.

INTRODUCTION

A link between the medial temporal lobe and memory function can be found in clinical case material more than a century ago (von Bechterew 1900), but the point became firmly established only when the profound effects of medial temporal lobe resection on memory were documented systematically by Brenda Milner in a patient who became known as H.M. (Milner 1972, Scoville & Milner 1957). At the time that H.M. was first described, the anatomy of the medial temporal lobe was poorly understood, and it was not known what specific damage within this large region was responsible for H.M.'s memory impairment.

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Ultimately, an animal model of human memory impairment was developed in the nonhuman primate (Mishkin et al. 1982, Squire & Zola-Morgan 1983). Cumulative behavioral work with the animal model over a 10-year period, together with neuroanatomical studies, succeeded in identifying the anatomical components of the medial temporal lobe memory system (Squire & Zola-Morgan 1991): the hippocampal region (the CA fields, the dentate gyrus, and the subicular complex) and the adjacent entorhinal, perirhinal, and parahippocampal cortices that make up much of the parahippocampal gyrus. The anatomical studies described the boundaries and connectivity of these areas, initially in the monkey and subsequently in the rat (Burwell et al. 1995, Insausti et al. 1987, Lavenex & Amaral 2000, Suzuki & Amaral 1994). In outline, the hippocampus lies at the end of a cortical processing hierarchy, and the entorhinal cortex is the major source of its cortical projections. In the monkey, nearly two thirds of the cortical input to the entorhinal cortex originates in the adjacent perirhinal and parahippocampal cortices, which in turn receive widespread projections from unimodal and polymodal areas in the frontal, temporal, and parietal lobes as well as from retrosplenial cortex (Figure 1).

During the period in which this memory system was identified, it became understood that the system is specifically important for declarative memory (Schacter & Tulving 1994, Squire 1992). Declarative memory supports the capacity to recollect facts and events and can be contrasted with a collection of nondeclarative memory abilities including skills and habits, simple forms of conditioning, and the phenomenon of priming. What is acquired by nondeclarative memory is expressed through performance rather than recollection. Different forms of nondeclarative memory depend on the integrity of specific brain systems, including for example the neostriatum, the amygdala, and the cerebellum (Eichenbaum & Cohen 2001, Squire & Knowlton 1999).

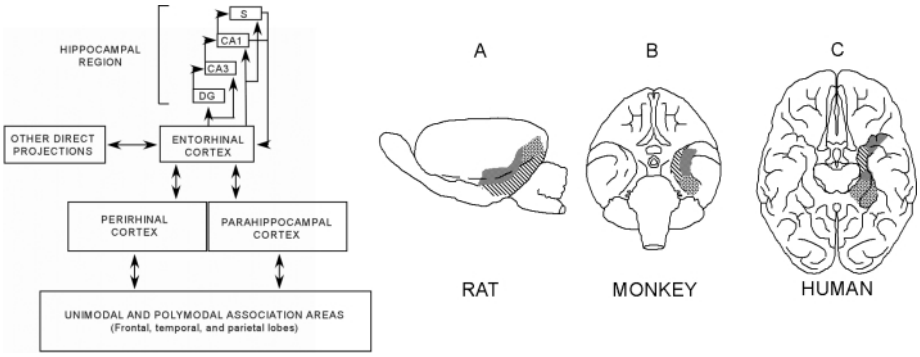

Figure 1 (*Left*) A schematic view of the medial temporal lobe structures important for declarative memory. S, subicular complex; DG, dentate gyrus; CA1, CA3, the CA fields of the hippocampus. (*Right*) Lateral view of the rat brain (*A*) and ventral views of the monkey (*B*) and human (*C*) brain showing the borders of perirhinal cortex (*gray*), entorhinal cortex (*diagonal stripes*), and parahippocampal cortex (*mottled shading*). In the rat, the parahippocampal cortex is termed postrhinal cortex. (Adapted from Burwell et al. 1996.)

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As a first approximation, one can say that all the structures of the medial temporal lobe contribute in some way to declarative memory. The evidence for this is twofold. First, patients with histological evidence of damage limited primarily to the hippocampal region (patients R.B., G.D., L.M., and W.H.; Rempel-Clower et al. 1996, Zola-Morgan et al. 1986) have a moderately severe memory impairment but one that is less severe than is found in patients with larger lesions that include the medial temporal cortex adjacent to the hippocampus (patients H.M and E.P.; Corkin et al. 1997, Stefanacci et al. 2000). Second, in systematic comparisons of monkeys with medial temporal lobe lesions, monkeys with limited hippocampal lesions were moderately impaired, whereas monkeys with lesions that included the hippocampal region as well as adjacent cortex were severely impaired (Zola-Morgan et al. 1994). These simple facts are not an argument for the idea that the structures of the medial temporal lobe must work together as a single and uniform functional unit (see Zola-Morgan et al. 1994), though this view has sometimes been attributed to us (e.g., Murray & Bussey 2001).

THE NATURE OF THE DISORDER

The hallmark of the impairment following medial temporal lobe lesions is profound forgetfulness. There are three important aspects of this condition. First, the impairment is multimodal. Memory is affected regardless of the sensory modality in which information is presented (Levy et al. 2003, Milner 1972, Murray & Mishkin 1984, Squire et al. 2001). This finding accords with the fact that the structures of the medial temporal lobe constitute one of the convergent zones of cortical processing and receive input from all the sensory modalities (Lavenex & Amaral 2000).

Second, immediate memory is intact. Even patients with large medial temporal lobe lesions have a normal digit span (Drachman & Arbit 1966). Further, when the material to be learned can be easily rehearsed (as in the case of 2 or 3 digits), retention may succeed even after several minutes (Milner et al. 1998). In contrast, when the material to be learned is difficult to rehearse (as in the case of complex designs), an impairment may be evident within 10 s (Buffalo et al. 1998).

Although intact immediate memory and impaired delayed memory are easy to demonstrate in humans, during the period that animal models were being developed it was a matter of some debate whether this same finding could be obtained in experimental animals (Horel 1994, Ringo 1991). Experimental work eventually established this point unambiguously (Alvarez et al. 1994, Clark et al. 2001, Overman et al. 1991). For example, rats with hippocampal lesions learned the delayed nonmatching-to-sample task at a normal rate using a short delay (4 s) between sample and choice (Clark et al. 2001). Yet performance was impaired when the delay was increased to 1 or 2 min. Further, during delayed testing, performance remained fully intact when 4-s delay trials were introduced intermittently, thereby indicating both retention of the nonmatching rule and intact short-term memory. Finally, even when extended training was given at a 1-min delay, exceeding the

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training given at the 4-s delay, performance remained intact at the short delay and impaired at the long delay.

The third notable aspect of the disorder is that memory impairment can occur against a background of intact perceptual abilities and intellectual functions. This finding is most unambiguous in patients with damage limited to the hippocampal formation (the hippocampal region plus entorhinal cortex) (Schmolck et al. 2000, 2002). Findings for patient H.M. are also relevant. Patient H.M. has bilateral damage to the hippocampal formation as well as perirhinal cortex, and he scores normally on intelligence tests as well as on many tests of perceptual function and lexical knowledge (Kensinger et al. 2001, Milner et al. 1968). It is true that H.M. exhibits mild impairment on a few tests of semantic knowledge (Schmolck et al. 2002), but H.M. has some bilateral damage to anterolateral temporal cortex, lateral to the medial temporal lobe (Corkin et al. 1997), and it is possible that the lateral damage is responsible for this impairment. Indeed, in patients with variable damage to lateral temporal cortex, the severity of impaired semantic knowledge was related to the extent of lateral temporal damage (Schmolck et al. 2002).

During the 1960s and 1970s, when human amnesia began to be widely and systematically studied, there was considerable interest in whether the disorder was principally one of storage or retrieval (cf. Squire 1982). The weight of the evidence since then has favored storage and the idea that the hippocampus and related structures are needed to establish representations in long-term memory. In the case of short-lasting episodes of severe memory impairment, such as transient global amnesia (Kritchevsky et al. 1988), the events that occur during the period of amnesia are not subsequently remembered after recovery from amnesia. New learning again becomes possible, but events from the amnesic episode itself do not return to memory. Accordingly, when the medial temporal lobe is damaged, representations in neocortex that are initially established in immediate memory must reach some abnormal fate. If the medial temporal lobe is not functional at the time of learning, memory is not established in a usable way and is not available later. The most direct evidence for this idea comes from combined single-cell recording and lesion work in monkey (Higuchi & Miyashita 1996; see below).

To take a storage view of memory impairment is not to suppose that the medial temporal lobe is the permanent repository of memory. Because remote memory is spared even in patients with large medial temporal lobe lesions (see Retrograde Memory), permanent memory must be stored elsewhere. For example, higher visual area TE, lateral to the medial temporal region, is thought to be a site for long-term, visual memory storage (Mishkin 1982, Miyashita 1993). The medial temporal lobe works in conjunction with area TE to establish long-term visual memory. In monkeys, changes in single-cell activity have been observed within the medial temporal lobe during and after the formation of long-term, associative memory (Messinger et al. 2001, Wirth et al. 2003, Naya et al. 2003), but it is not known how long such changes persist or for how long they may be needed for the expression of long-term memory.

It was also found that a signal appears in the medial temporal lobe during the recall of visual associative information. When monkeys performed an associative

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memory task (when A is presented as a sample, choose A′, not B; conversely, when A′ is presented as a sample, choose A, not C), perceptual signals (e.g., in response to stimulus A) were evident in area TE before they were evident in perirhinal cortex (Naya et al. 2001). In contrast, memory-retrieval signals, initiated during the short delay between the sample and the choice stimuli, appeared first in perirhinal cortex and then in TE. Further, lesions of perirhinal and entorhinal cortex abolished the ability of neurons in area TE to represent associations between stimulus pairs (Higuchi & Miyashita 1996). The implication is that neurons in area TE are part of long-term memory representations and that the connections from the medial temporal lobe to temporal neocortex are needed to maintain previously acquired representations and to establish new ones.

ALTERNATIVE VIEWS OF MEDIAL TEMPORAL LOBE CORTEX

Studies in the monkey have led to the proposal that severe memory impairment results not from damage to medial temporal cortex but from conjoint interruption of axons in the fornix, in fibers of passage through the amygdala, and in the temporal stem (Gaffan 2002). Yet, in patient H.M., the fornix and the temporal stem are almost entirely intact (Corkin et al. 1997). Further, histologically confirmed damage limited to the hippocampal formation can cause clinically significant, disabling memory impairment despite sparing of amygdala, temporal stem, and fornix (patients G.D. and L.M.; Rempel-Clower et al. 1996). Also, temporal stem white matter lesions in monkeys severely impair pattern discrimination learning (Zola-Morgan et al. 1982). Yet, the large medial temporal lobe lesions that established a model of amnesia in the monkey spare the learning and retention of pattern discriminations (Zola-Morgan et al. 1982). Humans with medial temporal lobe lesions can learn a two-choice discrimination in one or two trials, like normal individuals, but they then forget what they learned (Squire et al. 1988). In contrast, normal monkeys learn the pattern discrimination task gradually during several hundred trials in a manner reminiscent of skill learning (Iversen 1976). Accordingly, pattern discrimination learning in the monkey is better viewed as a task of nondeclarative memory (visual habit formation) (Mishkin et al. 1984). Pattern discrimination learning is dependent on an inferior temporal lobe–neostriatal pathway, and impaired pattern discrimination learning in the monkey does not model the impairment in human amnesia (Fernandez-Ruiz et al. 2001, Phillips et al. 1988, Teng et al. 2000).

Other work has asked whether perirhinal cortex supports primarily memory functions or whether it might also have a role in perceptual processing of visual information, for example, in the ability to identify complex objects (Buckley & Gaffan 1998, Buckley et al. 2001, Eacott et al. 1994). The proposal that perirhinal cortex is important for visual identification of objects is founded primarily on lesion studies in monkeys. Yet, it is difficult to test experimental animals for the ability to identify objects independent of their ability to learn about the objects

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(Bussey et al. 2003, Buffalo et al. 1999). Accordingly, some impairments attributed to a perceptual deficit could have resulted from impaired learning.

The perirhinal cortex lies medial and adjacent to unimodal visual area TE. The evidence that perirhinal cortex supports primarily memory functions comes, in part, from the sharp distinction that is found between the effects of perirhinal and TE lesions in the monkey (Buffalo et al. 1999). Perirhinal lesions cause multimodal (visual and tactual) memory impairment at long retention delays but not at short delays. In contrast, TE lesions cause visual (not tactual) memory impairment that appears even at very short retention delays, as would be predicted for a structure that supports visual information processing. For example, in the visual paired-comparison task, monkeys see two identical displays and then, after a variable delay, see the old display and a new one. Normal monkeys prefer to look at the new display, thereby indicating that they remember the familiar and, presumably less interesting, old display. At the shortest (1-s) delay, perirhinal lesions spared performance (66.4% preference for the new display; controls, 66.4%) but impaired performance at delays from 10 s to 10 min (56.6% preference; controls, 64.6%). In contrast, monkeys with TE lesions exhibited no preference at any delay (1 s to 10 min; 50.2% preference; chance = 50%).

Hampton & Murray (2002) systematically evaluated the perceptual abilities of monkeys with perirhinal lesions. Monkeys first acquired a number of visual discriminations and then were given probe trials to assess their ability to perform when the stimuli were manipulated. Monkeys with perirhinal lesions performed as well as controls when the stimuli were rotated (30°–120°), enlarged, shrunk, presented with color removed, or degraded with masks. The various manipulations did reduce performance, but performance was reduced to the same extent in operated and control animals.

When perceptual tasks were given to three patients with complete damage to perirhinal cortex bilaterally, performance was good on seven different discrimination tasks, including four that had revealed impairment in monkeys (Stark & Squire 2000). It is also notable that all three patients have some damage lateral to the perirhinal cortex, for example, in the fusiform gyrus and (for two of the patients) in inferolateral temporal cortex. Accordingly, some impairments found in these patients, for example, impairments in long-established semantic knowledge, may be due to lateral temporal damage rather than perirhinal damage (Schmolck et al. 2002). Indeed, this possibility seems likely, inasmuch as all three patients have complete damage to perirhinal cortex, but they differ in the severity of their semantic knowledge deficits and, correspondingly, in the extent of their lateral temporal damage.

The most recent proposal attributing perceptual functions to perirhinal cortex is more narrow than the idea that the perirhinal cortex is important for object identification or all perceptually difficult discriminations. Rather, the perirhinal cortex is proposed to be important for visual discriminations that have a high degree of feature ambiguity, that is, discriminations where a feature is rewarded when it appears as part of one object but not when part of another (Bussey et al. 2003). Yet, it is noteworthy that patient H.M. performs normally on a number of

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perceptual tasks, despite his extensive damage to perirhinal cortex (Milner et al. 1968). It would be useful to compare monkeys and patients with perirhinal damage on comparable tests of perceptual ability.

ACQUISITION OF KNOWLEDGE DESPITE SEVERE AMNESIA

Memory-impaired patients with medial temporal lobe lesions often have some capacity for learning about facts and events (Tulving et al. 1991, Westmacott & Moscovitch 2001). In these cases, the question of interest concerns the kind of learning that occurs. Is learning supported by whatever declarative memory remains and by residual medial temporal lobe tissue, or is some other kind of (nondeclarative) memory, and some other brain system, able to support performance?

In one study, the severely amnesic patient E.P. successfully acquired fact-like information in the form of novel three-word sentences, e.g., venom caused fever (Bayley & Squire 2002). Across 12 weeks and 24 study sessions, E.P. gradually improved his performance on both cued-recall tests (e.g., venom caused ???) and forced-choice tests. A number of observations indicated that what E.P. had learned was not factual knowledge in the ordinary sense. First, he never indicated that he believed he was producing correct answers, and he never made reference to the learning sessions. Second, his confidence ratings were the same for his correct answers as for his incorrect answers. Third, he failed altogether (1 of 48 correct) when the second word in each sentence was replaced by a synonym (venom induced ???). Thus, what E.P. learned was rigidly organized, unavailable as conscious knowledge, and in every respect exhibited the characteristics of nondeclarative memory, perhaps something akin to perceptual learning.

When medial temporal lobe damage is as extensive as it is in E.P. (Stefanacci et al. 2000), whatever fact-like learning can be acquired probably occurs directly in neocortex. Yet, there are many reported cases of less-severe memory impairment where patients successfully acquire factual information as declarative knowledge (i.e., patients are aware of what they have learned, and their confidence ratings are commensurate with their successful performance) (Hamann & Squire 1995, Shimamura & Squire 1988, Westmacott & Moscovitch 2001). In these cases, structures remaining intact within the medial temporal lobe are likely responsible for the successful learning.

DIVISION OF LABOR WITHIN THE MEDIAL TEMPORAL LOBE

There has been extended exploration of the possibility that different structures within the medial temporal lobe may contribute to declarative memory in different ways. Discussion of this issue properly begins with a neuroanatomical perspective. Information from neocortex enters the medial temporal lobe at different points.

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Thus, perirhinal cortex receives stronger projections from unimodal visual areas than does parahippocampal cortex, and parahippocampal cortex receives prominent projections from dorsal stream areas, including retrosplenial cortex, area 7a of posterior parietal cortex, and area 46 (Suzuki & Amaral 1994). Correspondingly, in monkeys, visual memory is more dependent on perirhinal cortex than on parahippocampal cortex (Squire & Zola-Morgan 1996), whereas spatial memory is more dependent on parahippocampal cortex (Malkova & Mishkin 2003, Parkinson et al. 1988). Similar results have been obtained in human neuroimaging studies, with the additional finding that the hippocampus is active in relation to both visual and spatial memory (Bellgowan et al. 2003).

The hippocampus is ultimately a recipient of convergent projections from these adjacent cortical structures, which are located earlier in the hierarchy of information processing. Accordingly, the hippocampus may have a special role in tasks that depend on relating or combining information from multiple sources, such as tasks that ask about specific events (episodic memory) or associative memory tasks that require different elements to be remembered as a pair (e.g., a name and a face). A related idea is that tasks that do not have these requirements, such as tasks that ask about general facts (semantic memory) or tasks that ask for judgments of familiarity about recently presented single items, may be supported by the cortex adjacent to the hippocampus (Brown & Aggleton 2001, Tulving & Markowitsch 1998). These ideas lead to two kinds of predictions. First, lesions limited to the hippocampus should disproportionately impair tasks of episodic memory and tasks of associative memory, relative to tasks of semantic memory or single-item memory. Second, limited hippocampal lesions should largely spare memory tasks that do not have these characteristics because such tasks can be supported by the perirhinal and parahippocampal cortices. Although these ideas have been prominent in discussions of medial temporal lobe function, the experimental work reviewed in the following sections provide little support for such sharp distinctions.

Episodic and Semantic Memory

The ability to acquire semantic memory has often been observed to be quite good, and better than the ability to acquire episodic memory, in single-case studies of memory-impaired patients (e.g., Hayman et al. 1993, Verfaellie et al. 2000). Because the general knowledge that makes up semantic memory can be based on multiple learning events, and because episodic memory is, by definition, unique to a single event, it is not surprising that semantic memory should usually be better than episodic memory. So long as memory impairment is not absolute, patients will always do better after many repetitions of material than after a single encounter, just as healthy individuals do. In the present context, one can begin with the observation that patients with limited hippocampal lesions have difficulty learning about single events. The question of interest is whether the acquisition of semantic information is also impaired when damage is limited to the hippocampal region.

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A recent study of five patients with limited hippocampal damage found marked deficits in knowledge about events in the news that occurred after the onset of amnesia (Manns et al. 2003b). Memory for remote events (11 to 30 years before amnesia) was intact, and time-limited retrograde amnesia was apparent during the several years before amnesia (see Retrograde Memory). A second study of the same patient group showed that impaired semantic memory was not an indirect result of impaired episodic memory. Healthy individuals were not aided in their recall of facts by being able to recollect episodic details about the circumstances in which they acquired their knowledge (Manns et al. 2003b). Other studies of smaller numbers of patients also found memory for facts to be impaired (Holdstock et al. 2002, Kapur & Brooks 1999, Reed & Squire 1998). Thus, semantic memory and episodic memory are both dependent on the hippocampal region.

Patients with developmental amnesia, who sustained limited hippocampal damage early in life, may provide an exception to this generalization (Baddeley et al. 2001, Vargha-Khadem et al. 1997). The best studied of these cases (Jon) has above-average intelligence and performs normally in language and other scholastic tests, despite having marked day-to-day memory problems since early childhood. It is possible that Jon's capacity for semantic learning is disproportionate to his ability to remember events from day to day, perhaps because early hippocampal damage (but not adult-onset amnesia) affords an opportunity for functional reorganization or compensation through learned strategies. However, an alternative possibility is that patients with developmental amnesia, given sufficient effort and repetition, may be able to acquire considerable semantic knowledge but only in proportion to what would be expected from their day-to-day episodic memory ability. Direct comparisons between adult-onset and developmental amnesia should clarify these issues.

Learning Associations and Learning Single Items

The idea that the ability to combine two unrelated items into memory depends more on the hippocampal region than the ability to learn single items has seemed plausible, and there is some support for this view (Kroll et al. 1996, Giovanello et al. 2003). Two other studies found that performance on these two kinds of tasks was similarly impaired. In the first study, patients saw a continuous stream of two-component stimuli (e.g., word pairs). On each trial, the item could be entirely novel (two new words), novel but with one repeated component (an old word and a new word), familiar but in a novel pairing (two old words recombined to form a new pair), or a true repetition (Stark & Squire 2003). The task was to endorse the true repetitions as having been encountered before and to reject the other items. In five separate experiments, patients with limited hippocampal lesions were impaired similarly across all item types. There was no suggestion that hippocampal damage selectively (or disproportionately) impaired the ability to reject recombined stimulus elements.

A second study evaluated the ability of the same patient group to remember faces, houses, or face-house pairs (Stark et al. 2002). The patients were impaired in

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all three conditions. To evaluate the severity of the impairment across conditions, the patients were allowed eight presentations of the study list instead of one. Their performance now matched control performance on both the single-item and the associative tests. Thus, the findings from these patient studies suggest that the hippocampus is similarly important for single-item and associative memory.

Recognition Memory: Recollection and Familiarity

One focus of discussion about possible division of labor within the medial temporal lobe has concerned recognition memory (the capacity to identify an item as one that was recently encountered). Recognition memory is widely viewed as consisting of two components, a recollective (episodic) component and a familiarity component. Recollection provides information about the episode in which an item was encountered, and familiarity provides information that an item was encountered but does not provide any knowledge about the learning context. It has been proposed that recollection depends especially on the hippocampus and that familiarity depends more on the adjacent cortex (Brown & Aggleton 2001, Rugg & Yonelinas 2003, Yonelinas 1998).

Studies of both humans and experimental animals are relevant to this proposal. In the case of patients with lesions limited to the hippocampal region, the remember/know technique has been used to assess recollection and familiarity, respectively. When a recently presented item evokes a recollection of the learning episode itself, one is said to remember. When a recently presented item is experienced simply as familiar, one is said to know (Tulving 1985). In one study of seven patients with limited hippocampal damage, the capacity for knowing was unmistakably impaired, and this impairment was as severe as the impairment in remembering (Manns et al. 2003a).

A disadvantage of the Remember/Know technique is that it is ultimately subjective, and there is disagreement about how reliably it can index recollection and familiarity (Donaldson 1996). Participants must judge the quality of what they retrieve, and how that judgment is made is open to interpretation by each participant. Perhaps the subjectivity of the method can explain why one patient with apparently limited hippocampal lesions (Holdstock et al. 2002), and three other memory-impaired patients for whom anatomical information was not available (Yonelinas et al. 2002; but see Wixted & Squire 2004), were reported to have a relatively preserved capacity for knowing (familiarity). Further work will be needed to decide this issue.

The distinction between recollection and familiarity is difficult, if not impossible, to apply to experimental animals because methods are not available in animals to reveal a capacity for the mental time travel that is central to episodic recollection (Tulving 2002; for a demonstration of episodic-like memory in scrub jays, see Clayton 1998). Nevertheless, it is of interest that studies of both monkeys and rodents have typically found recognition memory impairment following restricted hippocampal lesions (for monkeys, Beason-Held et al. 1999, Zola et al. 2000; for

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an exception in a study involving two-stage lesions and a different testing method, see Murray & Mishkin 1998). For rodents, the findings are rather clear when the lesions are sufficiently large and the retention delay is sufficiently long. Large hippocampal lesions impaired performance in the delayed nonmatching to sample task (Clark et al. 2001; Mumby et al. 1992, 1995, but see Mumby et al. 1996) and in the novel object recognition task (Clark et al. 2000, Gould et al. 2002). Similar findings were obtained after intrahippocampal injections of APV (Baker & Kim 2002) and in mice lacking the NMDAR-1 subunit in the hippocampal region (Rampon et al. 2000).

Impaired recognition performance has sometimes not been observed following subtotal hippocampal lesions (Gaskin et al. 2003), even in the same rats that exhibited impaired spatial learning in the standard water maze task (Duva et al. 1997). This finding can be potentially understood as an effect of lesion size. The water maze task is quite sensitive to hippocampal lesions. Damage to the dorsal hippocampus involving either 30% to 50% or 40% to 60% of total hippocampal volume severely impaired water maze performance (Broadbent et al. 2003, Moser et al. 1995). In contrast, neither a dorsal nor a ventral lesion that damaged 50% of total hippocampal volume affected performance on a recognition memory task (novel object recognition). Yet, as the hippocampal lesion increased in size from 50% to 100% of total hippocampal volume, a deficit gradually appeared, and the deficit was severe after a complete lesion (Broadbent et al. 2003).

These findings show that recognition memory in the rat depends on the integrity of the hippocampus, but less hippocampal tissue is needed to support object recognition than is needed to support spatial learning. Spatial memory tasks have much in common with tasks of free recall, and establishing a representation that can support unaided recall may require more hippocampal circuitry than establishing a representation sufficient to support recognition.

The novel object recognition task, as given to rodents, may be useful for considering the distinction between recollection and familiarity. In this task, animals initially explore two identical objects, and later they explore a new object and a copy of the old object. Recognition memory is demonstrated when animals explore the novel object more than the old object. This task depends on a spontaneous tendency to seek novelty and would seem to depend less on recollection of a previous event and more on the simple detection of familiarity. To the extent that rats and mice do base their performance in this task on the ability to discriminate between familiarity and novelty, the impairment in this task after hippocampal lesions provides direct evidence for the importance of the hippocampus in detecting familiarity.

Neurophysiology of Recognition

Recordings from single cells during recognition performance in rodents, monkeys, and humans are broadly consistent with the lesion data and also suggest ways in which the contribution of the hippocampus can be different than the contribution of adjacent cortex (Suzuki & Eichenbaum 2000). Neurons in perirhinal and entorhinal

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cortex typically respond in a stimulus-specific manner during recognition testing, modifying their firing rate if the stimulus is familiar rather than relatively novel (Suzuki et al. 1997, Young et al. 1997). In contrast, in the hippocampus, neurons tend to signal familiarity versus novelty irrespective of stimulus identity (that is, they provide an abstract recognition signal). These abstract recognition signals can report the familiar/novel status of single stimuli, or they can report the status of single stimuli in conjunction with other task features, such as the spatial position of the stimulus (conjunctive coding) (Wood et al. 1999).

These features of recognition signals in hippocampus and adjacent cortex are not absolute. Stimulus-specific responses can be found in the hippocampus, at least when relatively complex visual stimuli are used (Fried et al. 1997, Wirth et al. 2003). Thus, in humans, neurons in both hippocampus and entorhinal cortex responded selectively to faces and objects and also responded differently according to whether the stimulus was old or new (Fried et al. 1997). Most of the cells responded to familiarity in conjunction with other task features, such as the gender of a face or the facial expression.

The neurophysiological data suggest that all the anatomical components of the medial temporal lobe signal information relevant to recognition memory performance. The conjunctive recognition signals prominent in hippocampus and the stimulus-specific signals commonly found in adjacent cortex may contribute differently to recognition. It is also possible that both kinds of signals are needed to achieve intact recognition performance on most tasks. This possibility may explain why it has been difficult to demonstrate qualitatively distinct effects on recognition following damage to hippocampus or adjacent cortex.

NEUROIMAGING STUDIES OF THE MEDIAL TEMPORAL LOBE

During the past few years, there has been an explosion of interest in using neuroimaging techniques to study medial temporal lobe function and the possible division of labor within this region. While useful information has been obtained from neuroimaging studies, these techniques present certain challenges, which are useful to consider before reviewing recent findings. Principal among these are (*a*) the correlational nature of the data, (*b*) the lack of a true baseline, and (*c*) the technical problem of localizing results across participants to particular brain structures.

First, because neuroimaging techniques provide correlational data, neuroimaging cannot provide evidence about the necessity (or the importance) of a particular structure for a particular function. Early studies of eyeblink conditioning in the rabbit make this point nicely. Multiple-unit activity in the hippocampus develops robustly during delay conditioning in response to the conditioned stimulus, and this activity precedes and predicts the behavioral response (Berger et al. 1980). Yet, hippocampal lesions have no effect on the acquisition or retention of the

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conditioned response (Mauk & Thompson 1987, Schmaltz & Theios 1972). These findings show that the hippocampus is not important for this conditioned behavior, even though the hippocampus exhibits activity correlated with the behavior. Hippocampal activity would presumably prove itself important if measures of declarative memory were taken, for example, if the animal needed to report when or where the conditioning occurred. The work on eyeblink conditioning makes the simple point that the activity observed in a particular brain region in a neuroimaging study may be incidental to the task that individuals are performing. Further, greater activity in a particular region during task A than during task B does not necessarily mean that this region is more important for task A than for task B.

The second challenge is that neuroimaging techniques are contrastive, and the choice of control task (that is, the baseline task) can determine whether activity increases, decreases, or does not change in association with the task of interest (Gusnard & Raichle 2001). For example, when interspersed 3-s periods of rest were used as a baseline task, neither novel nor familiar scenes elicited activity in the hippocampal region (Stark & Squire 2001a). Yet, rest periods are times of active mental activity. If the rest condition were the only baseline available, one might conclude that familiar and novel pictures do not activate the hippocampus. However, when a tedious, repetitive task served as baseline (judging digits as odd or even), robust hippocampal activity was observed bilaterally in response to both familiar and novel scenes.

The third challenge is the need to accurately align activity in medial temporal lobe structures across participants. Traditional techniques that optimize whole-brain alignment [e.g., aligning to the atlas of Talairach & Torneaux (1988)] do not adequately account for variations in location and shape of medial temporal lobe structures. For example, if one overlays the medial temporal lobes from two brains, each of which has been segmented manually to identify subregions of the medial temporal lobe and then aligned to the Talairach atlas, about half of the voxels are segmented differently in the two brains. For example, a voxel may be segmented as entorhinal cortex in one brain and in perirhinal cortex or outside the medial temporal lobe in the other brain (Stark & Okado 2003).

Investigators have taken three approaches to this issue, all of which have advantages over simply aligning all brains to a common brain atlas (Talairach & Tournoux 1988). One method is to collapse activity for each participant across all the voxels that fall within anatomically defined regions of interest. A second method is to adapt cortical unfolding techniques to map data for each participant onto a two-dimensional map and then to align the individual maps (Zeineh et al. 2000). A third method is to align participants by maximizing the overlap of anatomically defined regions of interest (e.g. hippocampus, perirhinal, entorhinal, and parahippocampal cortex) at the expense of whole-brain alignment [the ROI-AL (region of interest-based alignment method); Stark & Okado 2003]. All three methods include the essential ingredient of identifying anatomical boundaries in individual brains rather than basing localization on where voxels end up after transforming each brain into a standard atlas.

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Specialization of Function Within the Medial Temporal Lobe

A theme of many early neuroimaging studies concerned whether encoding and retrieval are associated with distinct loci of activity in the medial temporal lobe. One complication in looking for such a contrast is that encoding occurs not only when items are first presented for study but also when the same study items and new (foil) items are presented together in a retrieval test. Indeed, activity in the hippocampus and adjacent cortex during retrieval predicts how well the new items will be remembered in a postscan memory test (Stark & Okado 2003). A second complication is that many of the relevant studies make only a coarse division between anterior and posterior regions of the medial temporal lobe so that it is difficult to relate findings to anatomical structures and connectivity.

Although the literature is somewhat mixed, the available work does not suggest any simple, large-scale division of labor for encoding and retrieval (Schacter & Wagner 1999). For example, in one study, encoding and retrieval of face-name pairs activated the full longitudinal axis of the hippocampus (aligned using anatomical ROIs), and the pattern of activity was similar during encoding and retrieval (Small et al. 2001). Further, in a study of picture recognition, both encoding and retrieval were associated with activity in the hippocampal region, the perirhinal cortex, and the parahippocampal cortex (aligned using the ROI-AL technique) (Stark & Okado 2003).

Distinct patterns of activity have sometimes been observed within the medial temporal lobe. In one study, activity was observed in perirhinal cortex during encoding of picture pairs but not during retrieval, whereas activity in the hippocampus and parahippocampal cortex was observed during both encoding and retrieval (Pihlajamäki et al. 2003). In another study, the above-mentioned unfolding technique was used to map activity related to encoding and retrieval of face-name pairs (Zeineh et al. 2003). Encoding but not retrieval was associated with above-baseline (fixation) activity in hippocampal fields CA2 and CA3 and in the dentate gyrus. It is unclear why activity was not observed in field CA1, which is an anatomical bottleneck essential to hippocampal function and to human memory (Zola-Morgan et al. 1986). In contrast, retrieval (and, to a lesser extent, encoding) was associated with above-baseline activity in the posterior subiculum. The right parahippocampal cortex also appeared to exhibit activity during encoding (Figure 3*A* in Zeineh et al. 2003). (For a finding of parahippocampal cortex and subiculum activity in encoding and retrieval, respectively, see Gabrieli et al. 1997). Additional studies using techniques that permit fine-scale anatomical distinctions will be useful. A continuing challenge for all such studies is the need to standardize test protocols and to use carefully selected baseline tasks so that specific aspects of memory and cognition can be isolated and findings can be compared across laboratories.

Another theme of recent neuroimaging studies has concerned the possibility that the hippocampal region (the CA fields, dentate gyrus, and subicular complex) may have identifiably distinct functions relative to the adjacent medial temporal cortex.

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For example, as discussed earlier, there has been interest in the idea that the hippocampal region might be especially active during the recollective or associative aspects of declarative memory. Accordingly, some studies have contrasted activity in the medial temporal lobe in association with "remember" responses and "know" responses, which are meant to index recollection and familiarity. Greater activity associated with "remember" than "know" responses may index the recollective aspects of declarative memory (but may also reflect simple differences in the amount of information retrieved or in one's confidence that what is retrieved is correct). Other studies contrasted activity associated with forming or retrieving associations (e.g., face-name pairs) with the activity associated with forming or retrieving single items (e.g., faces or names alone). Greater activity during the successful encoding of a face-name pair than during the successful encoding of a face and a name (but not their association) may index the formation of associations per se.

Although dissociations between recollective or associative memory and familiarity or single-item memory have been reported, the findings do not reveal a sharp distinction between the hippocampal region and adjacent cortex. Recent studies have implicated both the hippocampal region (Davachi et al. 2003; Dobbins et al. 2002; Düzel et al. 2003; Eldridge et al. 2000; Henke et al. 1997, 1999; Kirwan & Stark 2004, Ranganath et al. 2003, Small et al. 2001; Sperling et al. 2001a, 2003; Stark & Squire 2001b; Yonelinas et al. 2001) and the parahippocampal cortex (Davachi et al. 2003; Dobbins et al. 2002; Düzel et al. 2003; Eldridge et al. 2000; Henke et al. 1997, 1999; Ranganath et al. 2003; Kirwan & Stark 2004; Yonelinas et al. 2001) in recollective memory and in the encoding and retrieval of associations. Additionally, several studies have implicated the perirhinal cortex or the entorhinal cortex in these same processes (Dobbins et al. 2002, Düzel et al. 2003, Kirwan & Stark 2004, Pihlajämaki et al. 2003, Sperling et al. 2003). Accordingly, it would be an oversimplification to conclude that the hippocampal region has a specific or unique role in associative or recollective aspects of declarative memory. The same patterns of activity observed in the hippocampal region have been observed in adjacent cortex (most often in parahippocampal cortex). Likewise, it would be an oversimplification to conclude that the cortex adjacent to the hippocampus has a specific or unique role in nonassociative forms of declarative memory. Although there is evidence for nonassociative or familiarity-based activity in the entorhinal and perirhinal cortices (Dobbins et al. 2002, Davachi et al. 2003, Henson et al. 2003, Kirwan & Stark 2004, Ranganath et al. 2003), nonassociative or familiarity-based activity can also be observed in the parahippocampal cortex (Kirwan & Stark 2004) as well as in the hippocampal region (Henson et al. 2003, Small et al. 2001, Stark & Squire 2000, 2001b).

Thus, the considerable data available from recent neuroimaging studies do not lead to any simple conclusions about division of labor within the medial temporal lobe. Although activity in the hippocampal region has been correlated with the associative, recollective, and contextual aspects of declarative memory, activity in the posterior parahippocampal gyrus (parahippocampal cortex) has been correlated with these same aspects of memory. Further, although the perirhinal cortex has been

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linked to nonassociative (single-item) memory, this region is sometimes active as well in relation to associative memory. Lastly, activity in the hippocampal region has been correlated with nonassociative memory. Neuroimaging techniques present a number of challenges for the objective of illuminating the functional anatomy of memory. Future work will benefit from carrying out more rigorous anatomic localization. In addition, it is striking to what extent results can differ across studies that ostensibly attack the same problem, and it appears that almost any methodological variation will affect what is found. Gains can be obtained by reducing the differences between studies in design, test materials, and data analysis.

SPATIAL MEMORY

Since the discovery of hippocampal place cells in the rodent (O'Keefe & Dostrovsky 1971), an influential idea has been that the hippocampus creates and uses spatial maps and that its predominant function is to support spatial memory (O'Keefe & Nadel 1978). Place cells are best observed in empty environments. When a task is introduced, the same cells come to be activated in relation to the significant features of the task (Eichenbaum et al. 1999). In one study, more than half of the neurons that exhibited task-related activity fired in relation to nonspatial variables (Wood et al. 1999). It is also true that selective hippocampal lesions impair nonspatial memory in rodents (Bunsey & Eichenbaum 1996), monkeys (Doré et al. 1998), and humans (Squire et al. 2001, Levy et al. 2003). Accordingly, spatial memory can be viewed as a subset, a good example, of a broader category (declarative memory), with the idea that this broader category is the province of the hippocampus and related structures (Eichenbaum & Cohen 2001, Squire 1992).

The development of neuroimaging techniques and virtual reality environments has afforded the opportunity to study spatial learning and memory in humans in some detail. Learning one's way through a virtual environment (Hartley et al. 2003, Maguire et al. 1998, Shelton & Gabrieli 2002) or recalling complex routes through a city (Maguire et al. 1997) activated the posterior parahippocampal gyrus (parahippocampal cortex) and sometimes the hippocampus, as well. Activity was often bilateral, but sometimes right unilateral, presumably depending on the strategy that participants used during learning. These activations often appeared to be specifically spatial. For example, activation was greater during wayfinding than when following a well-learned path (Hartley et al. 2003), greater during route learning than when learning via an aerial view (Shelton & Gabrieli 2002), and greater when recalling spatial layouts and landmarks than when recalling nontopographical information (Maguire et al. 1997). These findings imply an important role of the parahippocampal cortex, and possibly hippocampus, in spatial memory. Alternatively, a more abstract formulation is also possible, namely, that the hippocampus is important in both spatial and nonspatial tasks where new information must be acquired and associated in ways that allow it to be used flexibly to guide behavior (McNamara & Shelton 2003).

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RETROGRADE MEMORY

Damage to the medial temporal lobe almost always results in some loss of memory for information acquired before the damage occurred. When damage is limited to the hippocampus, entorhinal cortex, or fornix, the retrograde memory impairment is temporally graded, impairing recent memory and sparing more remote memory. In the case of experimental animals, more than a dozen studies have demonstrated this phenomenon, typically across a time course of ∼30 days (see Squire et al. 2004). For example, in a study of trace classical eyeblink conditioning in the rat (Takehara et al. 2003), hippocampal lesions 1 day after learning nearly abolished the conditioned response, but the lesion had no effect after 4 weeks. In contrast, lesions of medial prefrontal cortex affected the conditioned response only marginally 1 day after learning but severely affected performance after 4 weeks and had an intermediate effect after 2 weeks. These findings are consistent with the results from 2-deoxyglucose studies following spatial discrimination learning in mice. Metabolic activity decreased in the hippocampus from 5 to 25 days after learning but increased in frontal, anterior cingulate, and temporal neocortex (Bontempi et al. 1999).

Temporal gradients of retrograde amnesia have also been well described in patients with damage limited to the hippocampal region (Kapur & Brooks 1999, Manns et al. 2003b). Here, the amnesia extends across a period of a few years rather than a few weeks and spares more remote memory. Interestingly, there is sparing of remote memory for facts (semantic memory) as well as sparing of remote episodic memory for autobiographical events (Bayley et al. 2003). In one study, 8 patients, including 2 with large medial temporal lobe lesions (E.P. and G.P.), and 25 age-matched controls attempted to recollect early memories, specific to time and place, in response to each of 24 different cue words (e.g., river, bottle). Overall, the recollections of the patients and the controls contained a similar number of details (±5%) and were comparable by several other measures as well. A few memory-impaired patients have been found to have difficulty recalling autobiographical episodes, even from their early life (Bayley & Squire 2003, Cipolotti et al. 2001, Moscovitch et al. 2000). In one study (Bayley & Squire 2003), such patients had significant reductions in brain volume in the frontal and/or temporal lobes. Therefore, it seems likely that, as the anatomy of memory-impaired patients comes to be described more completely, those who fail at remote autobiographical recollection will prove to have damage outside the medial temporal lobe.

Neuroimaging studies of retrograde memory have also been reported, but the results are mixed and difficult to interpret (Haist et al. 2001, Maguire et al. 2001, Maguire & Frith 2003, Niki & Luo 2002, Ryan et al. 2001). One difficulty is that, when individuals in the scanner are asked about an old memory that they have not thought about for some time, they can almost always, after the scanning session, remember whatever they were able to retrieve during the scanning session. Accordingly, activity observed during memory retrieval may be related not to retrieval but to the encoding of new information into long-term memory.

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The consolidation view of temporally graded retrograde amnesia begins with the principle that long-term memory is stored as outcomes of processing and in the same regions of neocortex that are specialized for what is to be remembered (Mishkin 1982, Squire 1987). By this view, the hippocampus initially works together with the neocortex to allow memory to be encoded and then to be accessible. Through a gradual process of reorganization, connections among the cortical regions are progressively strengthened until the cortical memory can be accessed independently of the hippocampus (McClelland et al. 1995, Squire & Alvarez 1995).

The available data appear to discount an alternative proposal, which states that the hippocampus and related structures are always necessary for recalling the richness of detail available in autobiographical recollections (Nadel & Moscovitch 1997). Furthermore, the alternative view proposes that temporal gradients are a byproduct of incomplete lesions. Yet, in experimental animals temporal gradients frequently have been reported after complete hippocampal lesions (Clark et al. 2002, Kim et al. 1995, Winocur et al. 2001).

One feature of human retrograde amnesia, scarcely explored in animal studies, is that retrograde memory loss is extensive when the damage includes not only hippocampus but also the adjacent cortex (Reed & Squire 1998). Thus, patient E.P. has intact recollections of his early life but nevertheless has retrograde amnesia covering several decades. One possibility is that the perirhinal and parahippocampal cortices do not have the temporary role in memory storage that has been attributed to the hippocampus itself. Physiological changes and changes in the distribution of divergent projections from TE have been described in perirhinal cortex after the learning of visual-paired associates (Naya et al. 2003, Yoshida et al. 2003), but it is not yet known whether these changes are needed to guide memory storage in the adjacent area TE (Higuchi & Miyashiata 1996) or whether these changes are themselves part of an essential long-term memory store. Interestingly, temporal gradients of retrograde amnesia have been reported in rats following selective lesions of perirhinal cortex (Kornecook et al. 1999, Wiig et al. 1996), and studies of larger lesions would be informative, for example lesions that include both hippocampus and postrhinal cortex.

One area of continuing uncertainty concerns the status of spatial memory following medial temporal lobe lesions. In humans, remote spatial memory is spared even following large medial temporal lesions. Thus, patient E.P. could recall the spatial layout of the region where he grew up and from which he moved away as a young adult more than 50 years earlier (Teng & Squire 1999; for a description of patient K.C., who could also navigate in his home environment, see Rosenbaum et al. 2000). E.P. performed as well as age-matched controls who had grown up in the same region and also moved away. He could mentally navigate, construct novel routes, and point correctly to landmarks while imagining himself at various locations. Yet E.P. has no knowledge of the neighborhood where he moved in 1993, after he became amnesic; and although he lives within two miles of the Pacific Ocean, he cannot when asked point in the direction of the ocean. These

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findings show that the human medial temporal lobe is needed to acquire new spatial knowledge but is not the repository of remotely acquired spatial maps.

The few studies available involving remote spatial memory in rodents have led to mixed results. Although two studies of rats with dorsal hippocampal lesions found evidence for sparing of remote spatial memory (64-day-old memory, Ramos 1998; 98-day-old memory, Kubie et al. 1999), in studies involving the most widely used test of spatial memory (the Morris water maze) remote spatial memory was impaired (Bolhuis et al. 1994, Mumby et al. 1999, Sutherland et al. 2001). One study (Clark et al. 2003) used three different tests of spatial memory: the standard water maze; the annular water maze, which removes the need for spatial navigation (Hollup et al. 2001); and a dry-land version of the water maze. In all three tasks, animals with large hippocampal lesions exhibited impaired spatial memory, even when the learning-surgery interval reached 98 days.

It is unclear why the findings for rodents differ from the findings in humans. One difference between the two kinds of studies is that spatial learning in rodents occurred during a limited period of time when the animals were adults, whereas the patient studies involved information acquired over many years while the patients were growing up. Studies of spatial learning in very young rodents would be informative. A second possibility is that typical tests of remote spatial memory in the rodent may require some new learning ability because the animal must continually update its location in space to succeed at the retention test (Knowlton & Fanselow 1998). In contrast, patients do not need to acquire new information in order to answer questions about their remote spatial memory. Additional work with reversible lesions in rodents, introduced early or late after learning, should be useful in resolving this issue (Riedel et al. 1999).

CONCLUSION

Study of the medial temporal lobe and memory is benefited by the possibility of addressing similar questions in humans, monkeys, and rodents using a variety of techniques: lesions, neuroanatomical tract-tracing, neuroimaging, single-cell recording, and manipulation of gene expression. Many questions are currently under debate, but the clearest path to settling these questions, and answering the next ones, lies in approaches that begin with thorough anatomical information about lesions, neuroimages, and electrode sites. Promising directions include parallel lesion studies in patients and neuroimaging studies in healthy volunteers, parallel approaches to neuroimaging of humans and single-cell recording in monkeys, and genetic studies of mice that build on what is learned from humans and monkeys. In all these endeavors, there is a need for standardized behavioral test protocols as well as programs of work that build cumulatively from study to study. Two additional topics have not been considered here because the work is too new to fully appreciate its significance. The first topic is the phenomenon of neurogenesis in the dentate gyrus and its possible relevance to behavioral plasticity (Kemperman

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2002). The second topic is the concept of what has been newly termed reconsolidation (Nader et al. 2000), which revives older claims (Misanin et al. 1968) that reactivation of a consolidated memory can sometimes make information vulnerable to interference or disruption. These and many other topics will occupy students of memory in the years to come.

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