



Mechanisms of Memory

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Mechanisms of Memory

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Recent studies of animals with complex nervous systems, including humans and other primates, have improved our understanding of how the brain accomplishes learning and memory. Major themes of recent work include the locus of memory storage, the taxonomy of memory, the distinction between declarative and procedural knowledge, and the question of how memory changes with time, that is, the concepts of forgetting and consolidation. An important recent advance is the development of an animal model of human amnesia in the monkey. The animal model, together with newly available neuropathological information from a well-studied human patient, has permitted the identification of brain structures and connections involved in memory functions.

MOST SPECIES ARE ABLE TO ADAPT IN THE FACE OF EVENTS that occur during an individual lifetime. Experiences modify the nervous system, and as a result animals can learn and remember. One powerful strategy for understanding memory has been to study the molecular and cellular biology of plasticity in individual neurons and their synapses, where the changes that represent stored memory must ultimately be recorded (1). Indeed, behavioral experience directly modifies neuronal and synaptic morphology (2). Of course, the problem of memory involves not only the important issue of how synapses change, but

also questions about the organization of memory in the brain. Where is memory stored? Is there one kind of memory or are there many? What brain processes or systems are involved in memory and what jobs do they do? In recent years, studies of complex vertebrate nervous systems, including studies in humans and other primates, have begun to answer these questions.

Memory Storage: Distributed or Localized?

The collection of neural changes representing memory is commonly known as the engram (3), and a major focus of contemporary work has been to identify and locate engrams in the brain. The brain is organized so that separate regions of neocortex simultaneously carry out computations on specific features or dimensions of the external world (for example, visual patterns, location, and movement). The view of memory that has emerged recently, although it still must be regarded as hypothesis, is that information storage is tied to the specific processing areas that are engaged during learning (4, 5). Memory is stored as changes in the same neural systems that ordinarily participate in perception, analysis, and processing of the information to be learned. For example, in the visual system, the inferotemporal cortex (area TE) is the last in a sequence of visual pattern-analyzing mechanisms that begins in the striate cortex (6). Cortical area TE has been proposed to be not only a higher order visual processing region, but also a repository of the visual memories that result from this processing (4).

The idea that information storage is localized in specific areas of the cortex differs from the well-known conclusion of Lashley's classic work (7) that memory is widely and equivalently distributed throughout large brain regions. In his most famous study, Lashley showed that, when rats relearned a maze problem after a cortical

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lesion, the number of trials required for relearning was proportional to the extent of the lesion and was unrelated to its location. Yet Lashley's results are consistent with the modern view if one supposes that the maze habit depends on many kinds of information (for example, visual, spatial, and olfactory) and that each kind of information is separately processed and localized. Indeed, the brain regions, or functional units, within which information is equivalently distributed may be very small (5, 8). Thus, memory is localized in the sense that particular brain systems represent specific aspects of each event (9), and it is distributed in the sense that many neural systems participate in representing a whole event.

The Neuropsychological-Neural Systems Approach

One useful strategy for learning about the neural organization of memory has been to study human memory pathology. In some patients with brain injury or disease, memory impairment occurs as a circumscribed disorder in the absence of other cognitive deficits. Careful study of these cases has led to a number of insights into how the brain accomplishes learning and memory (10–12). Moreover, animal models of human amnesia have recently been developed in the monkey (4, 13) and rat (14). Animal models make it possible to identify the specific neural structures that when damaged produce the syndrome, and they set the stage for more detailed biological studies.

It has been known for nearly 100 years that memory is impaired by bilateral damage to either of two brain regions—the medial aspect of the temporal lobe and the midline of the diencephalon. Damage to these areas makes it difficult to establish new memories (anterograde amnesia) as well as to retrieve some memories formed before the onset of amnesia (retrograde amnesia). General intellectual capacity is intact, as is immediate memory (for example, the ability to repeat correctly six or seven digits), language and social skills, personality, and memory for the remote past, especially childhood. Because amnesia can occur against a background of normal cognition, the severity of the condition is often underappreciated. For example, patient N.A. (an example of diencephalic amnesia) became amnesic in 1960 after an accident with a miniature fencing foil (15). Radiographic evidence later identified a minimal area of damage in the left mediodorsal thalamic nucleus (16). This patient is a pleasant

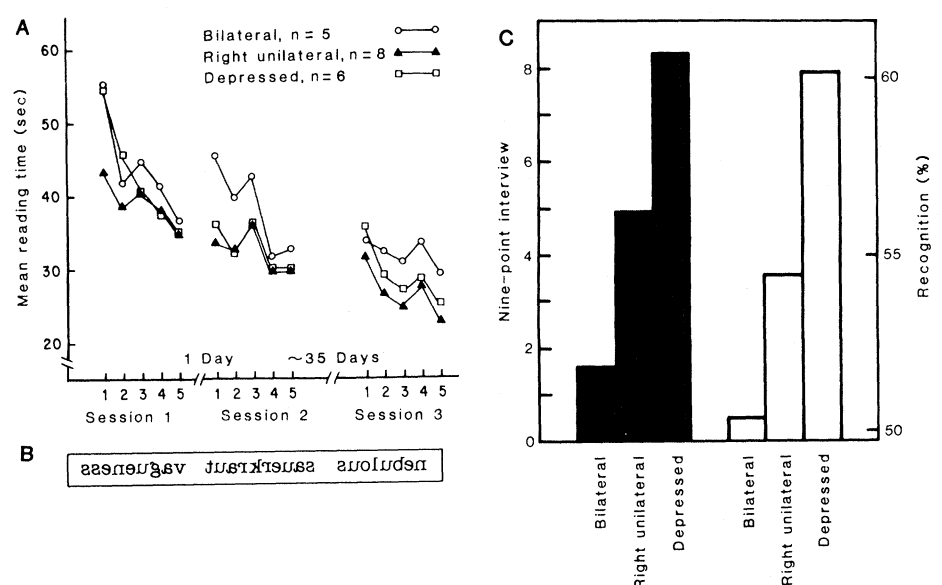
man with an agreeable sense of humor, who could join in any social activity without special notice. However, he would be unable to learn the names of his colleagues, or keep up with a developing conversation, or speak accurately about public events that have occurred since his injury. He has an intelligence quotient (IQ) of 124, can make accurate predictions of his own memory abilities (17), and has no noticeable impairment of higher cognitive functions except a severe verbal memory problem.

Medial temporal amnesia is best illustrated by the noted amnesic patient H.M. (18), who sustained a bilateral resection of the medial temporal lobes in 1953 in an effort to relieve severe epileptic seizures. Since that time, H.M. has exhibited profound anterograde amnesia, forgetting the events of daily life almost as fast as they occur. His defect in memory extends to both verbal and nonverbal material, and it involves information acquired through all sensory modalities. Other etiologies of amnesia have also contributed useful information, including Korsakoff's syndrome (19), electroconvulsive therapy (20), anoxia and ischemia (21), and encephalitis (22).

Short-Term and Long-Term Memory

The study of amnesia has provided strong evidence for distinguishing between a capacity-limited immediate (sometimes called short-term) memory, which is intact in amnesia, and more long-lasting (long-term) memory, which is impaired (10, 23). Amnesic patients can keep a short list of numbers in mind for several minutes if they rehearse them and hold their attention to the task. The difficulty comes when the amount of material to be remembered exceeds what can be held in immediate memory or when recovery of even a small amount of material is attempted after an intervening period of distraction. Immediate memory is independent of the medial temporal and diencephalic regions damaged in amnesia. One possibility is that immediate memory is an intrinsic capacity of each cortical processing system (24). Thus, temporary information storage may occur within each brain area where stable changes in synaptic efficacy (long-term memory) can eventually develop. The capacity for long-term memory requires the integrity of the medial temporal and diencephalic regions, which must operate in conjunction with the assemblies of neurons that represent stored information.

Fig. 1. Learning and retention of a mirror-reading skill despite amnesia for the learning experience (25). (A) Patients prescribed bilateral or right unilateral ECT and depressed patients not receiving ECT practiced mirror-reading during three sessions on three different days (three words per trial, 50 trials per session). The time required to read each word triad aloud during each block of ten trials provided the measure of mirror-reading skill. The first ECT of the prescribed series intervened between practice sessions 1 and 2. An average of seven ECT's and a total of 35 days intervened between practice sessions 2 and 3. (B) Sample word triad from the mirror-reading test. (C) At the beginning of session 3, subjects were tested for their recollection of the previous learning sessions (nine-point interview) and for their ability to recognize the words they had read (chance, 50%).



Declarative and Procedural Knowledge

In addition to a distinction between short-term and long-term memory functions, recent findings suggest a further distinction within the domain of long-term memory. The memory deficit in amnesia is narrower than previously thought in that not all kinds of learning and memory are affected. Amnesic patients (i) demonstrate intact learning and retention of certain motor, perceptual, and cognitive skills and (ii) exhibit intact priming effects: that is, their performance, like that of normal subjects, can be influenced by recent exposure to stimulus material. Both skill learning and priming effects can occur in amnesic patients without their conscious awareness of prior study sessions and without recognition, as measured by formal tests, of the previously presented stimulus material.

Skill learning has been studied in subjects being taught to read words that are mirror-reversed (25). For normal subjects, the ability to read mirror-reversed words improved gradually during 2 days of practice and was then maintained at a high level for more than a month. Skill learning in amnesia was studied in psychiatric patients whose memories were temporarily impaired as a result of a prescribed course of electroconvulsive therapy (ECT). Patients im-

proved their mirror-reading skill at a normal rate and later retained the skill at a normal level (Fig. 1). Yet the same patients, unlike control subjects, could not recognize the words that they had read during the training sessions, and often they could not recall the training experience at all. Other kinds of amnesic patients also exhibit intact learning and retention of the mirror-reading skill (26).

Priming can be tested by presenting words and then providing the first three letters of the words as cues (27). The instructions determine the outcome (28). When subjects are instructed to use the three-letter fragments (each of which can form at least ten common words) as cues to retrieve recently presented words from memory, normal subjects perform better than amnesic patients. Amnesic patients perform normally only when subjects are directed away from the memory aspects of the task and are asked instead to complete each three-letter fragment to form the first word that comes to mind (Fig. 2).

Intact priming effects in amnesia can also be demonstrated in free association tests (29) and when recently presented words are cued by category names (30). For example, when the word *baby* had been presented, the probability was more than doubled that this word would later be elicited by instructions to free associate a single response to the word *child* (Fig. 2). In fact, priming effects in amnesia can be fully intact even when attempts to recall the words from memory fail altogether (29) and when multiple-choice recognition memory is no better than chance (31). Thus priming effects seem to be independent of the processes of recall and recognition memory. In the word-completion task, the words seem to "pop" into mind, yet amnesic patients are unable to recognize them as familiar. Studies of normal subjects have also emphasized the differences between priming and standard recall and recognition tests (32).

These results have suggested a distinction between information based on skills or procedures and information based on specific facts or data. This distinction is reminiscent of earlier accounts in philosophy and psychology of how knowledge is represented (33). The terms "procedural" and "declarative" (34) describe the kinds of information that amnesic patients can and cannot learn (12, 35). The distinction reflects the operation of two kinds of memory processes or systems. Declarative memory is explicit and accessible to conscious awareness, and it includes the facts, episodes, lists, and routes of everyday life. It can be declared, that is, brought to mind verbally as a proposition or nonverbally as an image. It includes both episodic memory (specific time-and-place events) as well as semantic memory (facts and general information gathered in the course of specific experiences) (36, 37). Declarative memory depends on the integrity of the neural systems damaged in amnesia as well as on the particular neural systems that store the information being learned.

In contrast, procedural knowledge is implicit, and it is accessible only through performance, by engaging in the skills or operations in which the knowledge is embedded. Procedural learning may depend in some cases on the participation of the extrapyramidal motor system (38). In priming, preexisting representations are activated (39), and the information that is acquired is implicit and has other characteristics of procedural knowledge (40). Priming effects may depend exclusively on intact cortical representations because they are reduced in patients with dementia resulting from early stage Alzheimer's disease, but not in amnesic patients with equivalently severe memory problems and not in patients with dementia resulting from Huntington's disease (41).

Priming effects are distinct from declarative memory in two other important respects. (i) The information acquired by priming is fully accessible only through the same sensory modality in which material was presented initially (30). More complex information learned by amnesic patients sometimes has this same feature; that is, it is

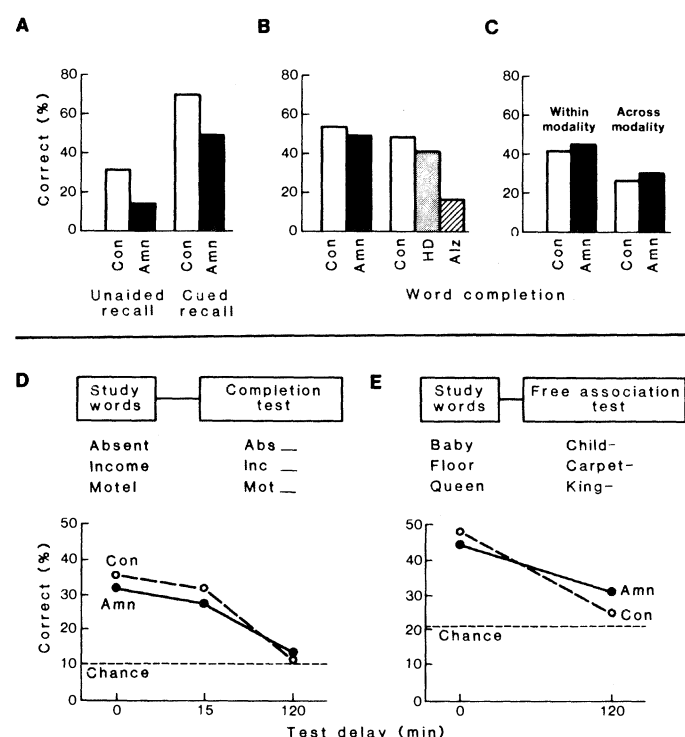


Fig. 2. Intact priming effects in amnesia (28–30, 41). Subjects studied words like those in (D) and (E) and then were tested in one of several ways. (A) Amnesic (Amn) patients were impaired at unaided recall and at cued recall, where the first three letters of the study words were given as cues. (B) Amnesic patients exhibited normal word completion effects (priming), where they completed each three-letter fragment with the first word that came to mind. Amnesic patients produced the study words as frequently as control (Con) subjects (chance, 10%). Patients with dementia resulting from Huntington's disease (HD) also exhibited intact priming effects, but priming effects were reduced in patients with dementia due to early-stage Alzheimer's disease (Alz). (C) When the study words and the three-letter fragments were presented in different sensory modalities (auditory-visual) rather than the same modality (visual-visual), priming effects were attenuated. (D) Priming effects were transient. (E) Amnesic patients exhibited normal free association (semantic priming) effects. (B and E) The amnesic patients were patients with Korsakoff's syndrome, $n = 7$ or 8 ; (A, C, and D) the amnesic patients were patients with Korsakoff's syndrome, $n = 7$ or 8 , plus two cases of anoxic or ischemic amnesia. Control subjects, $n = 8$ to 20 ; Huntington's disease, $n = 8$; Alzheimer's disease, $n = 8$.

inflexible, and the correct responses are accessible only if precisely the same stimuli that were used during learning are presented (42). (ii) Priming effects are short-lived in both amnesic patients and control subjects, declining to baseline in about 2 hours. When the task has only one common solution (for example, *juice* for *ju-* or *assassin* for *a--a--in*), normal subjects exhibit word completion effects that last for days or weeks. However, amnesic patients exhibit such effects for only a few hours (43). It may be easy for normal subjects to use ordinary memory strategies in these circumstances. At the same time, priming might well last longer under more natural conditions, such as when subjects have frequent encounters with the same stimuli.

A number of considerations suggest that procedural learning is phylogenetically old. It may have developed as a collection of encapsulated, special-purpose learning abilities (44). Memory was then realized as cumulative changes stored within the particular neural systems engaged during learning. By this view, some simple forms of associative learning, which occur in invertebrates (45) and are prominently developed in mammals (46), are examples of procedural learning. These would be expected to be fully available to amnesic patients (47). In contrast, the capacity for declarative knowledge is phylogenetically recent, reaching its greatest development in mammals with the full elaboration of medial temporal structures, especially the hippocampal formation and associated cortical areas. This capacity allows an animal to record and access the particular encounters that led to behavioral change. The stored memory is flexible and accessible to all modalities.

The evidence thus supports the idea that the brain has organized its memory functions around fundamentally different information storage systems (Fig. 3). This notion necessarily accepts the concepts of conscious and unconscious memory as serious topics for experimental work. In most cases the same experience would engage both memory systems. For example, perception of a word transiently activates the preexisting assembly of neural elements whose conjoint activity corresponds to that perception. This activation subserves the priming effect, an unconscious process that temporarily facilitates processing of the same word and associated words. The same stimulus also establishes a longer lasting declarative, and conscious, memory that the word was seen, and seen at a particular time and place, through participation of the neural systems within the medial temporal and diencephalic regions.

Memory Consolidation and Retrograde Amnesia

Memory is not fixed at the moment of learning but continues to stabilize (or consolidate) with the passage of time. When this concept was first advanced in 1900 (48), strong support for it was found in the phenomenon of temporally graded retrograde amnesia (49). For example, when rats or mice are given electroconvulsive shock (ECS) after training, they later exhibit impaired memory for the training experience. As the interval between learning and ECS increases, the severity of retrograde amnesia decreases. In these studies, memory was usually susceptible to disruption from a few seconds to several minutes after initial learning (50). A number of treatments given shortly after learning, including drugs and hormones, can also influence the strength of memory (51). In contrast to these data from laboratory animals, clinical observations of human amnesia have suggested that temporally graded retrograde amnesia can have a much longer time scale (52). Thus, although the facts of retrograde amnesia support the idea that memory changes or consolidates after learning, it has been difficult to determine exactly what consolidation is or how long it lasts.

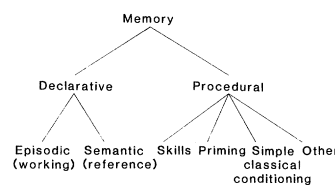


Fig. 3. A tentative taxonomy of memory. Declarative memory includes episodic and semantic memory (36), as well as the related terms, working and reference memory (91). Declarative memory can be retrieved explicitly as a proposition or image. Procedural memory includes skills, priming effects, simple classical conditioning (47), habituation, sensitization, and perceptual aftereffects, instances where what has been learned can be expressed only through performance as changes in the facility of specific cognitive operations.

More recent findings have elaborated the concept of memory consolidation and brought the data from experimental animals and from humans into register. These findings suggest that memory consolidation is a dynamic feature of long-term, declarative memory. Consolidation can proceed for as long as several years, during which time memory depends on the integrity of the neural systems that have been damaged in amnesic patients (53). One relevant finding was that, in humans, temporal gradients of retrograde amnesia longer than 1 year could be substantiated with formal tests. Patients prescribed ECT were given a test about television programs that had been broadcast for only one season during the past 16 years. The use of popularity ratings and other criteria permitted the test to be designed so that past time periods could be sampled equivalently (54). Before ECT, patients exhibited a forgetting curve across the time period sampled by the test, performing best for recent time periods and worst for remote ones. One hour after the fifth treatment, at a time when verbal IQ was intact, memory was selectively impaired for programs that had broadcast 1 to 2 years previously. Memory for older programs was normal (55). Temporally limited retrograde amnesia after ECT has also been demonstrated with other remote memory tests (56, 57).

Continuity between studies in humans and in experimental animals was established by a study of retrograde amnesia in mice, which used multiple, spaced ECS to mimic the treatment associated with extensive retrograde amnesia in humans (Fig. 4). Four ECS treatments produced a graded impairment for one-trial passive avoidance learning that covered 1 to 3 weeks (58). Thus, in mice, memory for the one-trial experience persisted for at least 12 weeks,

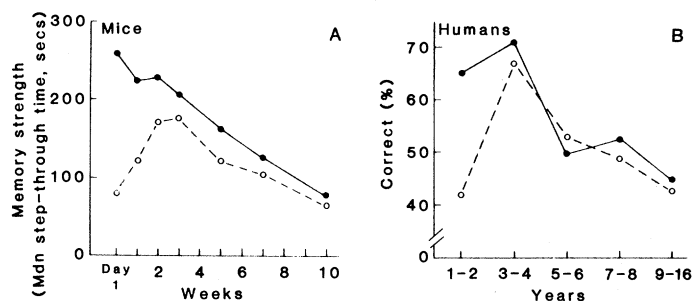


Fig. 4. Temporally limited retrograde amnesia in mice given ECS and in depressed psychiatric inpatients prescribed ECT (55, 58). (A) Mice were given a single training trial and then ECS or sham treatment (four treatments at hourly intervals) at one of seven times after training (1 to 70 days). Retention was always tested 2 weeks after ECS. (B) Patients were given a test about single-season television programs (from 1 to 16 years old) before the first and after the fifth in a prescribed course of bilateral ECT. In both cases, the abscissa shows the age of the memory at the time of treatment. Symbols: ●, normal forgetting; ○, retrograde amnesia. Abbreviation: Mdn, median.

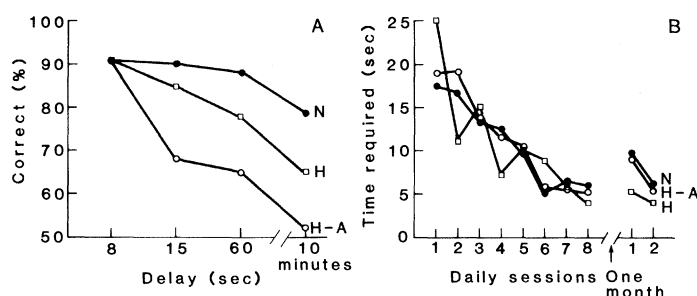


Fig. 5. Impaired recognition memory and intact skill learning in monkeys with medial temporal lesions (78, 80, 82, 92). (A) Eight normal (N) monkeys, eight with hippocampal (H) lesions, and four with conjoint hippocampal-amygdaloid (H-A) lesions were tested on the trial-unique, delayed nonmatching-to-sample task (93), a test of recognition memory analogous to tests failed by human amnesic patients. To obtain a raisin reward, monkeys chose the novel one of two objects, the familiar one having been presented alone 8 seconds to 10 minutes previously. H lesions impaired recognition memory, but conjoint H-A lesions produced a more severe impairment. Each data point is the average of 100 trials. (B) Three monkeys in each group learned to obtain a candy Lifesaver by maneuvering it along a metal rod and around a 90° bend. The rate of learning (six trials per session) was identical in the three groups, and retention was identical after a 1-month delay.

and memory grew resistant to disruption during the first few weeks after training. In humans, memory for television programs persisted for more than 16 years, and memory remained susceptible to disruption for a few years after initial learning. In both cases, retrograde amnesia covered a significant portion of the lifetime of the memory. Thus, initial acquisition of information was followed by two parallel events: gradual forgetting and gradually developing resistance to disruption of what remained.

These findings suggest that memory consolidation is neither an automatic process with a fixed lifetime nor a process that is determined entirely at the time of learning. Consolidation best refers to a hypothesized process of reorganization within representations of stored information, which continues as long as information is being forgotten. Memory is affected by rehearsal and by subsequent memory storage episodes. These events may influence the fate of recent, and unconsolidated, memories by remodeling the neural circuitry underlying the original representation. As time passes, some parts of the initial representation could be lost through forgetting, while other parts become more stable and coherent. In this sense, neural ensembles representing stored information could continually reorganize as they accommodate new information. The process of memory storage and consolidation may be competitive (5), in the same way that competition among axons occurs in the developing nervous system (59). Dynamic and presumably competitive changes have also been described in the representation of the hand in adult primate sensorimotor cortex after both deprivation and selective experience (60).

In patients with known brain lesions, the processes of memory storage and consolidation can be related to the medial temporal region. In particular, remote memory tests have demonstrated that in some amnesic patients retrograde amnesia is temporally limited, affecting only events that occurred during the years immediately preceding the onset of amnesia. For example H.M., who has bilateral medial temporal lesions, exhibits amnesia extending from a few years to perhaps 11 years before his surgery in 1953 (18, 61). He can both produce well-formed autobiographical episodes and also recall information about public events that occurred before surgery. Other patients with medial temporal amnesia [for example, patient R.B. (62)], are reported to have no measurable retrograde amnesia, or perhaps 2 or 3 years of retrograde amnesia, despite

marked anterograde amnesia. Some patients exhibit prolonged and extensive retrograde amnesia (22, 63), but damage beyond the medial temporal region has either been demonstrated in these instances or can be reasonably presumed.

Because amnesic patients have access to many premorbid memories, even to the extent that the quality and detail of their recall cannot be distinguished from that of normal recall (64), the medial temporal region cannot be a permanent memory storage site. For the same reason, the deficit seen in amnesia cannot be a general impairment in retrieval. The medial temporal region would seem to do its job during the time of learning and during some or all of the lengthy period of consolidation. Thus, for a period after learning, the storage of declarative memory and its retrieval depend on an interaction between the neural systems damaged in amnesia and memory storage sites located elsewhere in the brain (4, 5, 65). This interaction is thought to maintain the organization of an ensemble of distant and distributed memory storage sites until the coherence of these sites has become an intrinsic property of the ensemble. If the interaction is disrupted, the ability to acquire new declarative memory is impaired, and recently acquired memories that have not fully consolidated are lost. After sufficient time has passed, at least some memories no longer require the participation of the medial temporal region.

In amnesic patients with diencephalic lesions, the nature of anterograde and retrograde amnesia is less clear. For example, patients with Korsakoff's syndrome exhibit, instead of a temporally limited retrograde amnesia, a severe and extensive impairment of remote memory that covers most of their adult lives (57, 66). One possibility is that amnesia is a unitary deficit affecting both the establishment of new memories and the retrieval of old ones and that the deficit is qualitatively the same regardless of which part of the system is damaged (67). According to this view, the extensive remote memory deficit observed in Korsakoff patients is correlated with and predicted by the severity of their anterograde amnesia. Another possibility is that remote memory impairment is dissociable from the remainder of the memory disorder (68) and that extensive remote memory impairment is caused by additional neuropathology beyond that required to produce anterograde amnesia. This idea is supported by the near-zero correlation ($r = 0.04$) between anterograde amnesia and remote memory impairment in patients with Korsakoff's syndrome (69); by the finding that patient N.A., an example of diencephalic amnesia with a presumably circumscribed lesion, has little remote memory impairment (57, 64); and by the finding that patient H.M. has better remote memory than Korsakoff patients, despite having a more profound anterograde amnesia (61).

More data are needed to better understand the significance of extensive remote memory impairment. It seems reasonable to suppose that the typical Korsakoff patient has more widespread neuropathology than other amnesic patients under study. A list of cognitive deficits has accumulated in recent years—deficits that are particularly frequent in this patient group, but not in others, and that are unrelated to the severity of anterograde amnesia. These include (i) failure to release from proactive interference (70, 71)—that is, the normal improvement in performance does not occur when subjects attempt to learn words belonging to a new category after attempting several word lists from another category; (ii) a disproportionately large impairment in making judgments about temporal order (71); (iii) impaired metamemory skills—that is, inability to monitor and predict one's own memory performance (17); (iv) source amnesia in some Korsakoff patients (37)—that is, the successful recall of previously learned information without memory for when or where the information was acquired [also see (72)]. The question is whether remote memory impairment should be added to this list.

Animal Models and the Neuroanatomy of Memory

Careful descriptions of amnesia have helped to define the particular memory function that is damaged and have led to other useful information about how memory is organized in the brain. Yet to understand how the brain actually accomplishes learning and memory, it is essential to identify the specific brain structures that when damaged produce amnesia. This information must then be guided by neuroanatomy to specify a functional brain system consisting of the identified structures and their connections. Clinicopathological material from amnesic patients has generally identified where damage must occur in the brain to produce amnesia: the medial temporal region, with emphasis on the hippocampus; and the midline diencephalic region, with emphasis on the mediodorsal thalamic nucleus and the mammillary nuclei. However, this information has not established precisely which structures and connections are important. Patients frequently have brain lesions in addition to those that cause amnesia. Moreover, patient material seldom includes both detailed neuropathological data and quantitative behavioral information.

Because of the recent development of an animal model of human amnesia in the monkey (4, 13), as well as the neuroanatomical information now available about the relevant brain regions in the monkey (73), these issues can now be studied systematically. Several behavioral tests of memory that are sensitive to human amnesia have been adapted for the monkey, and memory performance from different studies can be quantified and compared. At the same time, in other animal models progress has been made at identifying where in the brain memory is stored (74).

With regard to amnesia and the medial temporal region, interest has focused recently on both the hippocampus and the amygdala. The amygdaloid complex is linked directly and reciprocally to both sensory-specific and multimodal cortical association areas. Afferent and efferent cortical pathways also communicate with the hippocampal formation (75), albeit indirectly through polysensory adjacent regions including the temporal pole, perirhinal cortex, and especially the parahippocampal gyrus. These extensive and widespread connections to the cortex are precisely what is needed if the medial temporal lobe is to have access to sites of information processing and memory storage.

Monkeys with bilateral lesions of the amygdala and hippocampal formation, which included perirhinal cortex and parahippocampal gyrus, exhibited severe memory impairment (Fig. 5). This lesion was intended to reproduce the surgical removal sustained by the amnesic patient H.M. As in human amnesia, the memory deficit in monkeys occurred in both visual and tactual modalities (76), and it was exacerbated by distracting the animals during the retention interval (77). Moreover, as in human amnesia, the same monkeys that were diagnosed as amnesic by these measures acquired perceptual-motor skills normally. They also learned normally skill-like

cognitive tasks such as pattern discrimination learning, which, like motor skills, involve stimulus repetition and incremental learning over many trials (78, 79). Monkeys with lesions of the "temporal stem," a fiber system that lies superficial to the hippocampus, were not amnesic (78, 80). This fiber system links temporal neocortex with subcortical regions, and it had been proposed to be the critical structure damaged in medial temporal lobe amnesia (81).

Studies in monkeys have also evaluated the effects on memory of separate hippocampal lesions that included dentate gyrus, subicular cortex, most of the parahippocampal gyrus, and posterior entorhinal cortex (76, 82–84) (Fig. 5). Although hippocampal lesions produced a clear memory impairment, the impairment was still larger after the combined hippocampal-amygdaloid lesion. Recent work suggests that the deficit in the combined lesion group may depend on removal of the amygdala together with the adjacent structures typically included in amygdala surgery (entorhinal and perirhinal cortex) (84, 85).

One recent proposal is that the critical structures are the hippocampus and amygdala and their diencephalic targets, the anterior nucleus of the thalamus and the mediodorsal thalamic nucleus, respectively (4). Bilateral medial thalamic lesions, including lesions limited to the posterior portion of the mediodorsal thalamic nucleus, cause a moderately severe memory impairment (86, 87). Such a proposal is compatible with a role in the same functional system for structures with strong anatomical connections to the medial temporal region and the medial thalamus, such as the mammillary nuclei (88), ventromedial frontal cortex (89), and basal forebrain (90). However, further studies are needed to quantify and compare the impairment that follows removal of these and other candidate structures. The amnesic syndrome is not an all-or-none phenomenon, and its severity can vary with the structure or combination of structures that are damaged.

Although animal studies are essential, they cannot illuminate the clinical significance of the observed memory impairments unless the severity of the impairments can be understood in terms of human memory dysfunction. For example, the hippocampus has long been linked to human memory impairment, though there have been few if any well-documented cases of amnesia with damage limited to this structure. Monkeys with hippocampal lesions do have a clear memory impairment. Would this correspond to a substantial memory impairment in humans or only a minor one?

Our laboratory recently obtained extensive clinicopathological information from a patient who developed amnesia at the age of 52 after an ischemic episode (62). Until his death 5 years later, he was tested extensively as part of our neuropsychological studies of memory and amnesia. He exhibited marked anterograde amnesia (Fig. 6), little if any retrograde amnesia, and no signs of cognitive impairment other than memory. His score on the Wechsler Adult Intelligence Scale (WAIS) was 111, and his Wechsler Memory Scale (WMS) score was 91. In normal subjects the WMS score is equivalent to the WAIS IQ, and the difference between the two

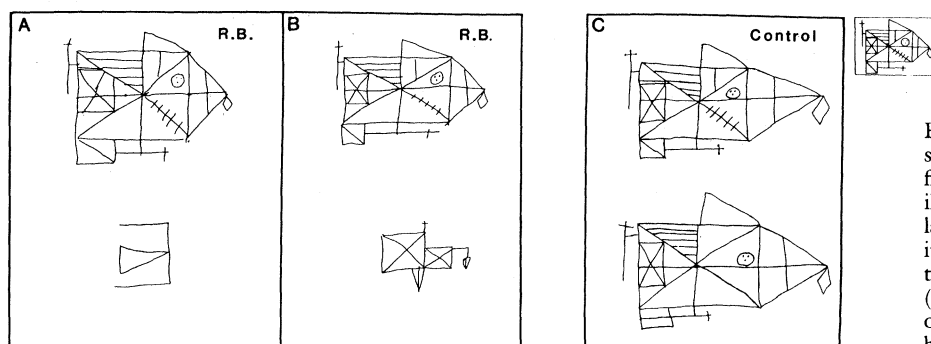


Fig. 6. Performance by amnesic patient R.B. on two separate administrations of the Rey-Osterrieth complex figure test (94). R.B. was asked to copy the figure illustrated to the upper right. Then 10 to 20 minutes later, without forewarning, he was asked to reproduce it from memory. (A) R.B.'s copy (top) and reproduction (bottom) 6 months after the onset of his amnesia. (B) His copy and reproduction 23 months after the onset of amnesia. (C) Copy and reproduction by a healthy control subject (62).

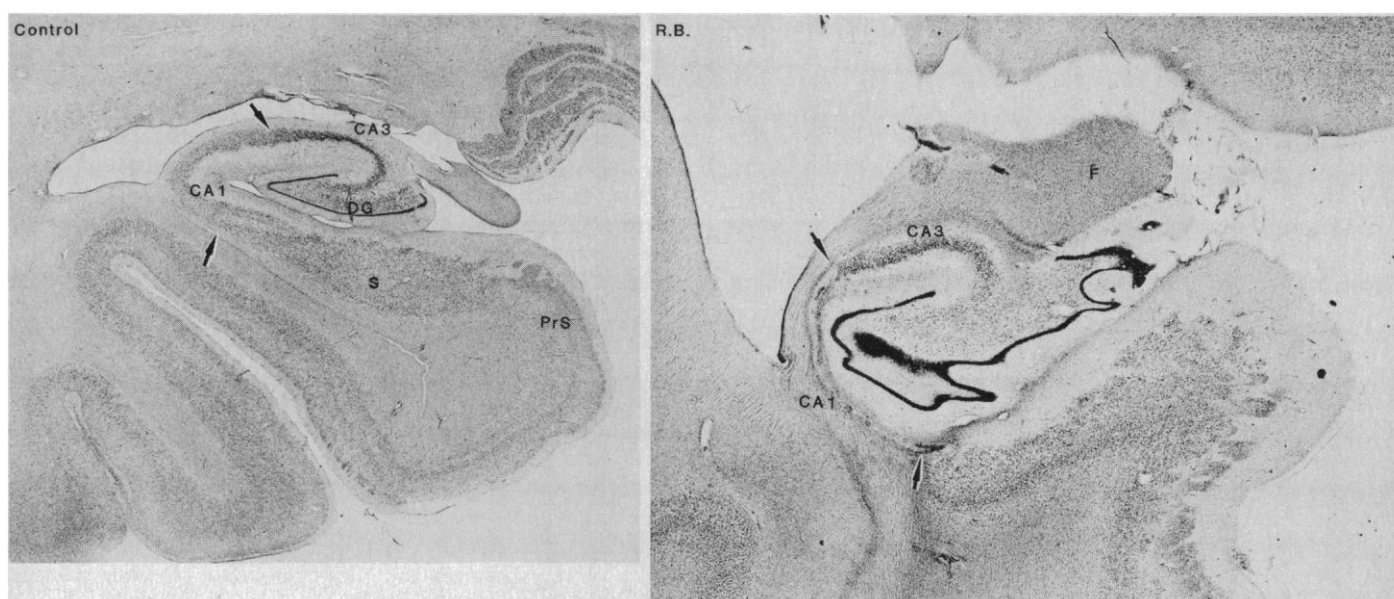


Fig. 7. Photomicrographs of thionin-stained, coronal sections through the hippocampal formation of a normal control brain (left) and patient R.B.'s brain (right). R.B. developed an amnesic syndrome in 1978 after an ischemic episode. He died in 1983 at the age of 57. Histological examination revealed a bilateral lesion involving the entire CA1 field of the hippocampus. In the control section, the two arrows indicate the limits of the CA1 field. In R.B.'s brain, the only pathology evident in the hippocampal formation was a

complete loss of pyramidal cells from the CA1 field (between the arrows). The amygdala, mammillary nuclei, and mediodorsal thalamic nucleus were normal, and there was no other significant pathology that could reasonably account for the memory impairment. Abbreviations: PrS, presubiculum; S, subiculum; CA1 and CA3, fields of the hippocampus; DG, dentate gyrus; F, fimbria of the fornix. (62)

scores provides one index of the severity of memory impairment. Thorough histological examination revealed a circumscribed bilateral lesion of the CA1 field of the hippocampus that extended its full rostral-caudal length but not beyond (Fig. 7). Some additional minor pathology was found (for example, left globus pallidus, right postcentral gyrus, and patchy loss of cerebellar Purkinje cells), but the only damage that could be reasonably associated with the memory defect was the hippocampal lesion.

Although the lesion was spatially limited, it affected an estimated 4.6 million pyramidal cells and would be expected to have a profound impact on the function of the hippocampus. A lesion in the CA1 field interrupts the essentially unidirectional flow of information that begins at the dentate gyrus and ends in the subicular complex and entorhinal cortex. These structures are the main sources of output from the hippocampus to subcortical, limbic, and cortical structures. Thus, a CA1 lesion would significantly disrupt the interaction between the hippocampus and memory storage sites, an interaction presumed to be critical for the storage and consolidation of declarative memory.

Conclusion

In neuroscience, questions about memory have often been focused at the cellular and molecular level—for example, how do synapses change when memory is formed? In psychology, memory has often been studied as whole behavior, without reference to the brain, and as a problem of what computations learning and memory require. This article describes what can be learned from an intermediate, neuropsychological level of analysis, which focuses on the brain processes and brain systems involved in learning and memory. Study of animals with complex nervous systems, including humans and other primates, has led to a view of memory and the brain that should have considerable generality across vertebrate species, and certainly across all mammals. The ultimate goal is to be able to move

across levels of analysis, from formal descriptions of cognition to underlying brain systems and finally to the neurons and cellular events within these systems. The problem of memory needs to be studied at all these levels, and should draw jointly on the disciplines of cognitive psychology, neuropsychology, and neurobiology.

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