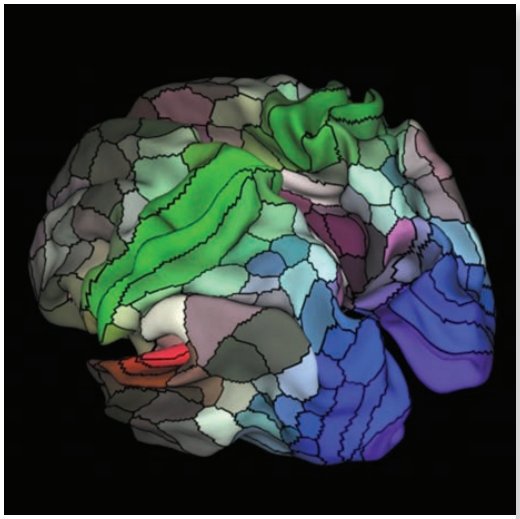
CHAPTER

30 Memory



Overview

IT SHOULD BE OBVIOUS THAT ONE OF THE MOST IMPORTANT of the brain's complex functions is the ability to store information from past experience and retrieve it, either consciously or unconsciously. Without this ability, access to the past and imagination of the future would be lost. *Learning* is the name given to the processes through which new information is acquired by the nervous system, and has already been addressed at the cellular level in the chapters on the mechanisms of the cellular and molecular plasticity of neuronal connections, the assumed basis for learning and memory (see Chapters 8 and 23–26). *Memory* is evident as recovered experiences that can be brought into consciousness (e.g., remembering what you ate for breakfast), or more often as changes in behavior (e.g., testing how much better you played a piece of music today as a result of yesterday's practice). For non-human animals, changes in behavior must suffice as evidence of memory, although behavioral changes are often taken to reflect conscious remembering, as in many non-human primate studies. Pathological loss of previously stored information (retrograde amnesia) and/or the inability to store new information (anterograde amnesia) have been especially instructive in understanding the neurological underpinnings of memory, a major challenge in modern neuroscience that has yet to be fully met. This chapter reviews the organization of human memory systems, surveys memory disorders and their implications, and considers some key questions about memory that remain unanswered.

Qualitative Categories of Human Memory

Humans have at least two qualitatively different ways of storing information, generally referred to as *declarative memory* and *nondeclarative memory* (Figure 30.1). **Declarative memory** is the storage and retrieval of material that is available to consciousness and can be expressed by language (i.e., "declared"). Examples of declarative memory are the ability to remember a phone number, the words to a song, or a past event. **Nondeclarative memory** (also referred to as **procedural memory**) is not available to consciousness, at least not in any detail. Such memories involve skills and associations that are generally acquired and retrieved at an unconscious level. Remembering how to shoot a basket or how to play the piano are examples of nondeclarative memories. It is difficult or impossible to describe exactly how we do these things, and thinking about how to carry out automatic activities may actually disrupt the ability to perform them efficiently. As discussed later in the chapter, the distinction between declarative and nondeclarative memory is well supported by anatomical, clinical, and other evidence.

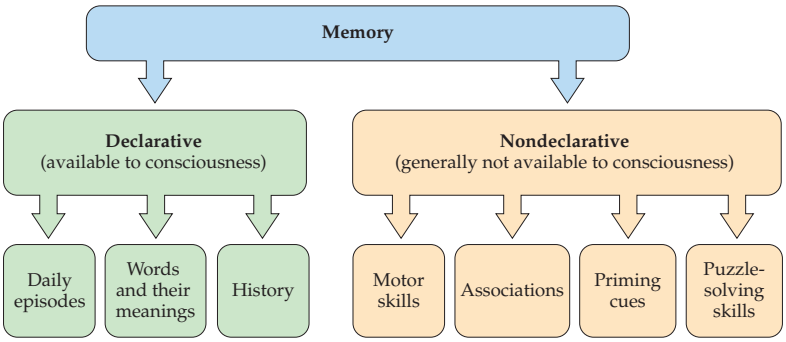


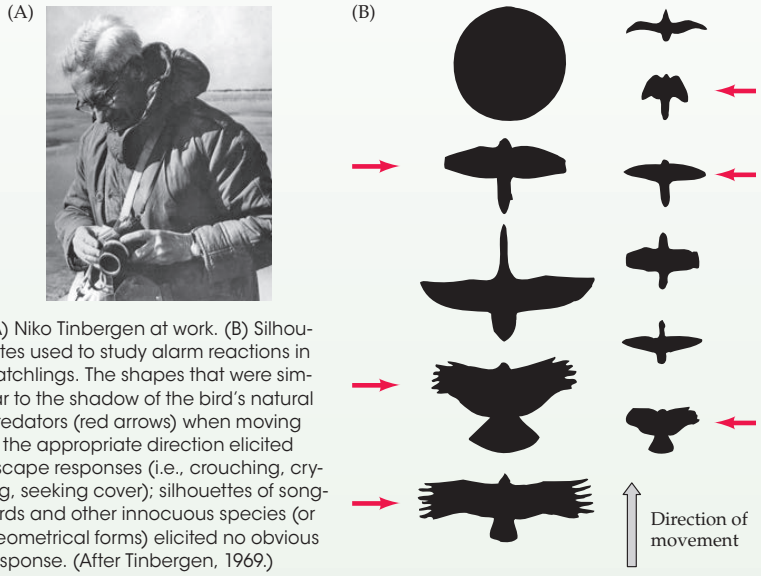
FIGURE 30.1 The major qualitative categories of human memory. Declarative memory includes those memories that can be brought to consciousness and expressed as remembered events, images, sounds, and so on. Nondeclarative, or procedural, memory includes motor skills, cognitive skills, simple classical conditioning, priming effects, and other information that is acquired and retrieved unconsciously.

BOX 30A ■ Phylogenetic Memory

A category of information storage not usually considered in standard accounts is that of memories arising from the experiences of a species over the eons, established by natural selection acting on the cellular and molecular mechanisms of neural development. Such stored information does not depend on postnatal experience but on what a given species typically encountered in its environment over evolutionary time. These "memories" are no less consequential than those acquired by individual experience and are likely to have much underlying biology in common with the memories established during an individual's lifetime; after all, both phylogenetic and ontogenetic memories are based on neuronal connectivity. In the former case, changing connectivity depends on natural selection, and in the latter, on the mechanisms of plasticity discussed in Chapters 8 and 25.

Information about the experience of the species, as expressed by endogenous or "instinctive" behavior, can be quite sophisticated, as is apparent in examples collected by ethologists for a wide range of animals, including primates. The most thoroughly studied instances of such behaviors are those occurring in young birds. Hatchlings arrive in the world with an elaborate set of innate behaviors. First is the complex behavior that allows the young bird to emerge from the egg. Once a bird has hatched, a variety of additional behaviors indicate how much of its early life is dependent on inherited information. Hatchlings of precocial species "know" how to preen, peck, gape their beaks, and carry out a variety of other complex acts immediately. In some species, hatchlings automatically crouch down in the nest when a hawk passes overhead but are oblivious to the overflight of an innocuous bird. Konrad Lorenz and Niko Tinbergen used handheld silhouettes to explore this phenomenon in naïve herring gulls, as illustrated in the figure shown here. "It soon became obvious," wrote Tinbergen, "that ... the reaction was mainly one to shape. When the model had a short neck so that the head protruded only a little in front of the line of the wings, it released alarm, independent of the exact shape of the dummy." Evidently, the memory of what the shadow of a predator looks like is built into the nervous system of this species. Examples in primates include the innate fear that newborn monkeys have of snakes and looming objects.

Despite the relatively scant attention paid to this aspect of memory, evolved and inherited neural associations are the most important component of the stored information in the brain that determines whether or not an individual survives long enough to reproduce.



(A) Niko Tinbergen at work. (B) Silhouettes used to study alarm reactions in hatchlings. The shapes that were similar to the shadow of the bird's natural predators (red arrows) when moving in the appropriate direction elicited escape responses (i.e., crouching, crying, seeking cover); silhouettes of songbirds and other innocuous species (or geometrical forms) elicited no obvious response. (After Tinbergen, 1969.)

Although it makes good sense to divide human learning and memory into categories based on the accessibility of stored information to consciousness, this distinction becomes problematic when considering learning and memory processes in non-human animals. From an evolutionary point of view, it is of course unlikely that declarative memory arose de novo in humans with the development of language. Although some researchers favor different classification systems for humans as opposed to other animals, studies suggest that similar memory processes operate in all mammals and that these functions are carried out by homologous neural circuitry. In non-human mammals, declarative memory typically refers to information that they are aware of, and could be "declared" if the species in question had this ability. Another criterion of declarative memory in non-human animals is its dependence on the integrity of the medial temporal lobes (see below). Nondeclarative memory, in humans and other animals alike, can be thought of as the acquisition and storage of neural associations that are not available to consciousness and not dependent on the medial temporal lobes.

Finally, and perhaps most important of all, are the memories we have as a result of the evolution of our species (Box 30A). Although such memories are not often considered, they represent changes in brain connectivity that have been wrought by millions of years of experience with behaviors that work and those that don't. Thus, we each come into the world with a vast array of inherited behaviors that far outweigh in value what we learn in the course of an individual lifetime.

Temporal Categories of Memory

Memory can also be categorized according to the time over which it is effective. Although the details are debated by both psychologists and neurobiologists, three temporal classes of memory are generally accepted (Figure 30.2). The first of these is **immediate memory**. By definition, immediate memory is the ability of the brain to hold onto ongoing experience for a second or so. For example, we normally make saccadic eye movements three or four times a second, thus continuously sending new "snapshots" of the visible environment to the visual system. Although we perceive the visual scene as stable, the snapshots are forgotten absent something arresting. Nonetheless, if you close your eyes at some random moment, immediately you can recall a good deal of information from the image you last saw.

Short-term memory, the second temporal category, is the ability to hold and manipulate information in the mind for seconds to minutes while it is being used to achieve a particular goal (such processes are also referred to as *working memory*). An everyday example is searching for a lost object; short-term memory allows the hunt to proceed efficiently, avoiding places already inspected. A conventional way of testing the integrity of short-term memory at the bedside is to present a string of random numbers, which the patient is then asked to repeat. The normal digit memory span is seven to nine numbers. Because short-term memory is limited in both duration and capacity, the relevant information must be rehearsed if it is to persist for a very long.

Short-term memory is also closely related to attention; indeed, it is sometimes considered to be a special category of attention that operates on internal representations rather than on sensory input as such. Short-term memory is also pertinent to language, reasoning, and problem solving, as the example of searching for a lost item makes plain. Thus, memory influences and is influenced by many other aspects of brain function. Although it is typically studied in the context of declarative memory, short-term memory also operates in the acquisition and ultimate storage of nondeclarative information.

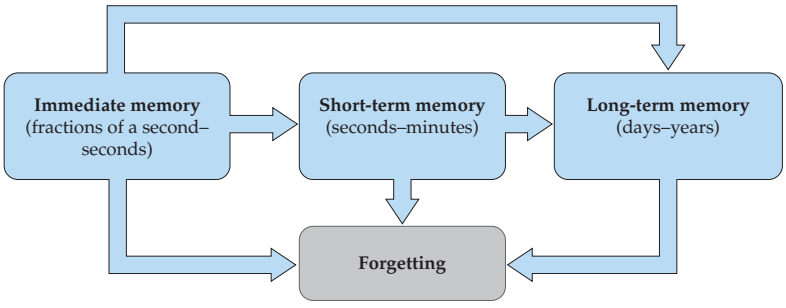


FIGURE 30.2 The major temporal categories of human memory. Information in both immediate and short-term memory can enter long-term memory, although most information is promptly forgotten.

The third temporal category is **long-term memory** and entails retaining information in a more permanent form of storage for days, weeks, or even a lifetime. Information of particular significance in immediate and short-term memory can enter into long-term memory by conscious or unconscious rehearsal or practice. There is general agreement that the so-called **engram**—the physical embodiment of any memory in neuronal machinery—depends on changes in the efficacy of synaptic connections and/or the actual growth and reordering of such connections. As discussed in Chapter 23, there is ample

evidence that mechanisms of synaptic change can and do act over each of the temporal intervals pertinent to the different endurances of memories. The term *consolidation* (Latin, "to make firm") refers to the progressive stabilization of memories that follows the initial encoding of memory "traces." Consolidation involves changes in gene expression, protein synthesis, and other mechanisms of synaptic plasticity that allow the persistence of memories at the cellular level and can be disrupted by interfering with these processes (see Chapters 8 and 23).

Priming

Another way of exploring the transfer of information from immediate and short-term memory to long-term memory is in terms of priming. **Priming** is defined as a change in the processing of a stimulus due to a previous encounter with the same or a related stimulus with or without conscious awareness of the original encounter. The phenomenon is typically demonstrated by presenting subjects with a set of items to which they are exposed under false pretenses. For example, a list of words can be given with the instruction that the subjects are to identify some feature that is actually extraneous to the experiment (e.g., identifying the words as verbs, adjectives, or nouns). Sometime thereafter (often the next day), the same individuals are given a different test in which they are asked to fill in the missing letters of words with the letters of whatever words come to mind (Figure 30.3) The test list actually includes fragments of words that were presented in the first test, mixed among fragments of words that were not. Subjects tend to fill in the letters to make the words that were presented earlier at a higher rate than expected by chance, and fill them in more quickly than they do new words, even though they may have little or no conscious memory of seeing the words from the earlier list.

The information stored by priming, however, is not particularly reliable. Consider the list of words in Table 30.1A. If the list is read to a group of students who are immediately asked to identify which of several items were on the original list and which were not (Table 30.1B), the result is surprising. Typically, about half the students report that the word *sweet* was included in the list in Table 30.1A; moreover, they are quite certain about it. The mechanism of such erroneous "recognition" is presumably the strong associations that have previously been made between the words on the list in Table 30.1A and the word *sweet*, which biases the students to think that *sweet* was a member of the original set. Clearly, memories, even those we feel quite confident about, are often false.

Priming is resistant to brain injury, aging, and dementia. As a result, its contributions are less obvious (and less

TABLE 30.1 ■ The Fallibility of Human Memory[a]

(A) Initial list of words		(B) Subsequent test list
candy	honey	taste
sour	soda	point
sugar	chocolate	sweet
bitter	heart	chocolate
good	cake	sugar
taste	eat	nice
tooth	pie	
nice		

[a]After hearing list A read aloud, subjects were asked to identify which items in list B had also been on list A. See text for the results.

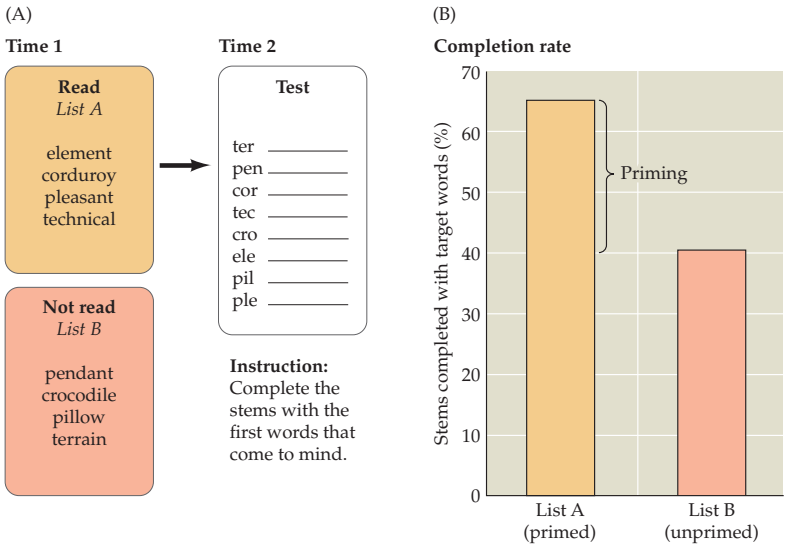


FIGURE 30.3 Priming. (A) In a commonly used test, the subject is presented at time 1 with a list of words to study (list A) and is later tested using a word-stem completion task (time 2). The stems could also be completed from list B, which comprises words the subject did not see during the initial session. (B) Subjects typically complete the stems with about 25% more studied than unstudied words; this percentage represents the effect of priming.

easily studied) than other forms of memory that are compromised by specific brain insults, such as impaired declarative memory following damage to the medial temporal lobes (see below). Among other things, priming shows that information previously presented is always influential, even though we are entirely unaware of its effect on subsequent behavior. The significance of priming is well known—at least intuitively—to advertisers, teachers, spouses, and others who want to influence the way we think and act.

The Importance of Association in Information Storage

The normal human capacity for remembering relatively meaningless information is surprisingly limited (as noted, a string of seven to nine numbers or other arbitrary items). This stated capacity, however, is misleading. People can remember 14 or 15 items in a briefly presented 5 × 5 matrix of 25 numbers or other objects if the experimenter points to specific boxes in the blank matrix during recall testing. Moreover, a person's digit memory span can be increased dramatically with practice. For example, a college student who for some months spent an hour each day being paid to successfully remember randomly presented numbers was able to recall a string of up to about 80 digits (Figure 30.4). He did this by making subsets of the string of numbers

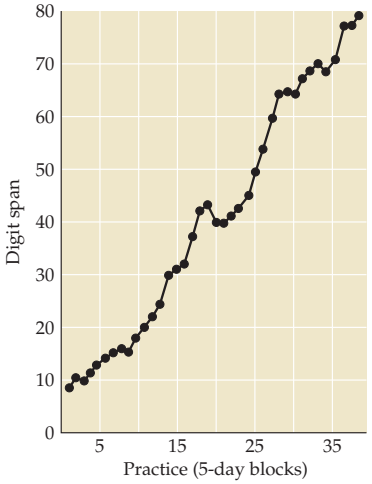


FIGURE 30.4 Increasing the digit span by practice and the development of associational strategies. During many months involving 1 hour of practice each day for 3 to 5 days a week, the subject increased his digit memory span from 7 to 79 numbers. Random digits were read to him at the rate of 1 per second. If a sequence was recalled correctly, 1 digit was added to the next sequence. (After Ericsson et al., 1980.)

he was given signify dates or times at track meets (he was a competitive runner)—in essence, giving meaningless items a meaningful context. This same strategy of enhancing associations is used by professional "mnemonists" who amaze audiences by prodigious feats of memory. A challenge for some mnemonists is memorizing as many as possible of the infinite number of digits in π (3.1416…*n*). The current world record is over 67,000 decimal places. The mnemonists who hold such records use a variety of strategies, a common one being associating the ten digits involved with musical notes and singing the number string.

The capacity of memory very much depends on what the information in question means to the individual and how readily it can be associated with information that has already been stored. A good chess player can remember the position of many more pieces on a briefly examined board than an inexperienced player, presumably because the positions have much more significance for individuals who understand the intricacies of the game (Figure 30.5). Arturo Toscanini, the late conductor of the NBC Philharmonic Orchestra, allegedly kept in his head the complete scores of more than 250 orchestral works, as well as the music and librettos for some 100 operas. Once, just before a concert in St. Louis, the first bassoonist approached Toscanini in some consternation, having just discovered that one of the keys on his bassoon was broken. After a minute or two of deep concentration, the story goes, Toscanini turned to the alarmed bassoonist and informed him that there was no need for concern, since that note did not appear in any of the bassoon parts for the evening's program. Such feats of memory are not achieved by rote learning but are a result of the fascination that aficionados bring to their special interests, sometimes in a pathological way (Box 30B).

Such examples indicate that motivation also plays an important role in memory. In one study of this issue, experimenters asked subjects to study a set of photographs that depicted either pieces of furniture or pieces of food (Figure 30.6). The subjects were later tested with a much larger set of photographs that included images from the previously studied set along with new ones; the subjects were asked to indicate whether a picture was "old" or "new." In one condition, the experimenters increased subjects' hunger by depriving them of food for several hours. Predictably, subjects were much more likely to remember more pictures of food when they were hungry than when they were not. There was no effect of motivation on memory for pictures of furniture.

Although few of us can boast the mnemonic prowess of a π enthusiast or a Toscanini, the human ability to remember the things that deeply interest us—whether baseball statistics, television show, or the details of brain structure—is nothing short of amazing.

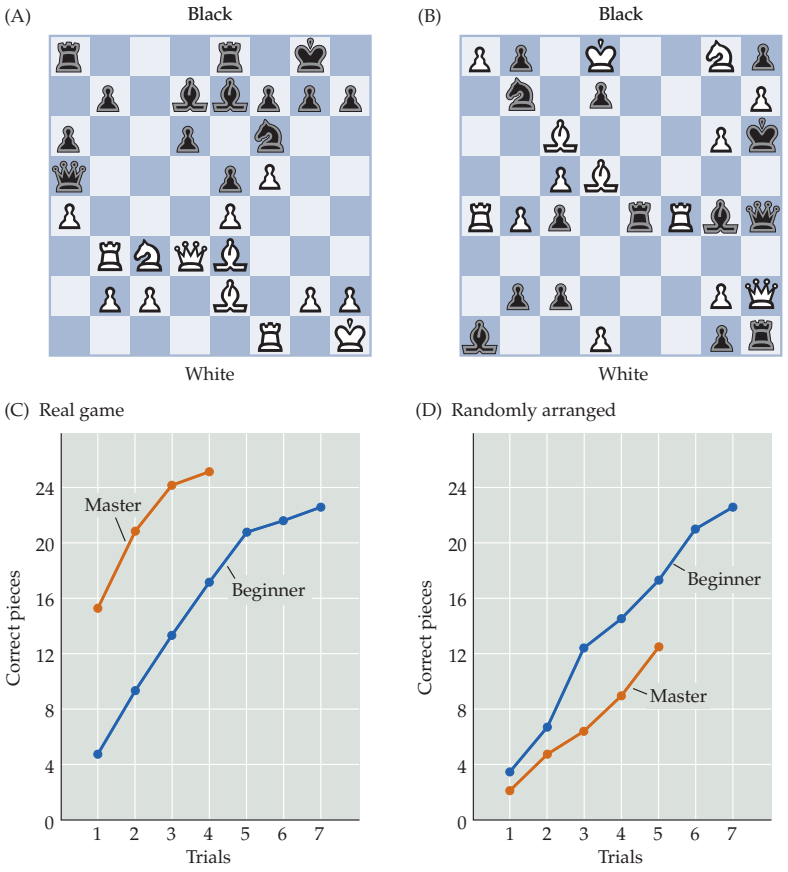


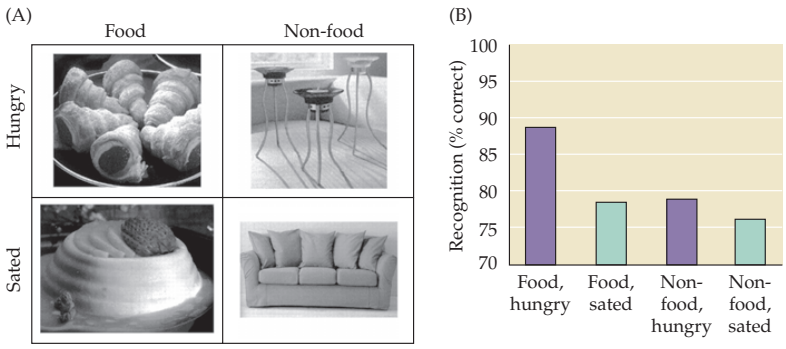
FIGURE 30.5 Retention of briefly presented information depends on past experience, context, and perceived importance. (A) Board position after white's 21st move in game 10 of the 1985 World Chess Championship between A. Karpov (white) and G. Kasparov (black). (B) A random arrangement of the same 28 pieces. (C,D) After briefly viewing the board from the real game, master players reconstruct the positions of the pieces with much greater efficiency than beginning players. With a randomly arranged board, however, beginners perform as well as or better than accomplished players. (After Chase and Simon, 1973.)

Conditioned Learning

Conditioned learning is defined as the generation of a novel response that is gradually elicited by repeatedly pairing a novel stimulus with a stimulus that normally elicits the response being studied. **Classical conditioning** occurs when an innate reflex is modified by associating its normal trigger with an unrelated stimulus; by virtue of the repeated association, the unrelated stimulus eventually triggers the original response. This type of conditioning was famously studied by the Russian psychologist Ivan Pavlov in experiments with dogs and other animals early in the twentieth century. The dogs' innate reflex was salivation (the *unconditioned response*) in reaction to the sight and/or smell of food (the *unconditioned stimulus*). The association was elicited in the animals by repeatedly pairing the sight and smell of food with the sound of a bell (the *conditioned stimulus*). The conditioned reflex was considered established when the conditioned stimulus (the sound of the bell) elicited salivation by itself (the *conditioned response*).

Operant conditioning refers to the altered probability of a behavioral response engendered by associating the response with a reward (or in some instances, a punishment). In Edward Thorndike's original experiments, carried out as part of his thesis work at Columbia University in the 1890s, cats learned to escape from a puzzle box by pressing the lever that opened the trap door to get a food reward. Although the cats initially pressed

FIGURE 30.6 Motivated memory. (A) Subjects studied a set of pictures of food and non-food (i.e., furniture) items and were later tested for their ability to discriminate the pictures they had seen from a new set of pictures. In one condition, subjects were made hungry by withholding food for several hours. (B) Memory for food items was significantly enhanced when subjects were hungry, but there was no significant effect of hunger on memory for non-food pictures. Results like these emphasize the importance of motivation and interest for memory performance. (From Morris and Dolan, 2001.)



BOX 30B ■ Savant Syndrome

A fascinating developmental anomaly of human memory is seen in rare individuals who until recently were referred to as *idiot savants*; the current literature tends to use the less pejorative phrase *savant syndrome*. Savants are people who, for a variety of poorly understood reasons (typically brain damage in the perinatal period), are severely restricted in most mental activities but extraordinarily competent and mnemonically capacious in one particular domain. The grossly disproportionate skill compared with the rest of their limited mental life can be striking. Indeed, these individuals—whose special talent may be in calculation, history, art, language, or music—are usually diagnosed as being severely impaired.

Many examples could be cited, but a summary of one such case suffices to make the point. The individual whose history is summarized here was given the fictitious name "Christopher" in a detailed study carried out by psychologists Neil Smith and Ianthi-Maria Tsimpli. Christopher was discovered to be severely brain damaged at just a few weeks of age (perhaps as the result of rubella during his mother's pregnancy or anoxia during birth; the record is uncertain in this respect). He had been institutionalized since childhood because he was unable to care for himself, could not find his way around, had poor hand–eye coordination, and had a variety of other deficiencies. Tests on standard IQ scales were low, consistent with his general inability to cope with daily life. Scores on the Wechsler Scale were, on different occasions, 42, 67, and 52.

Despite his severe mental incapacitation, Christopher took an intense interest in books from the age of about 3, particularly those providing factual information and lists (e.g., telephone directories and dictionaries). At about age 6 or 7 he began to read technical papers that his sister sometimes brought home from work, and he showed a surprising proficiency in foreign languages. His special talent in the acquisition and use of language (an area in which savants are often especially limited) grew rapidly. As an early teenager, Christopher could translate from—and communicate in—a variety of languages in which his skills were described as ranging from rudimentary to fluent; these included Danish, Dutch, Finnish, French, German, modern Greek, Hindi, Italian, Norwegian, Polish, Portuguese, Russian, Spanish, Swedish, Turkish, and Welsh. This extraordinary level of linguistic accomplishment is all the more remarkable since he had no formal training in language even at the elementary school level, and could not play tic-tac-toe or checkers because he was unable to grasp the rules needed to make moves in these games.

The neurobiological basis for such extraordinary individuals is not understood. It is fair to say, however, that savants are unlikely to have ability in their areas of expertise that exceeds the competency of normally intelligent individuals who focus passionately on a particular subject. Presumably, the savant's intense interest in a particular cognitive domain is due to one or more brain regions that continue to work reasonably well. Whether because of social feedback or self-satisfaction, savants clearly spend a great deal of their mental time and energy practicing the skill they can exercise more or less normally. The result is that the relevant associations they make become especially rich, as Christopher's case demonstrates.

the lever only occasionally—and more or less by chance—the probability of their doing so increased as the animals learned to associate this action with escape and reward. In Frederick Skinner's far more complete and better-known experiments performed a few decades later at Harvard, pigeons or rats learned to associate pressing a lever with receiving a food pellet in a widely used device that came to be known as a Skinner box (Figure 30.7). In both classical and operant conditioning, it takes a number of trials for the conditioning to become established. If the conditioned animal performs the desired response but the reward is no longer provided, the conditioning gradually disappears, a phenomenon called *extinction*.

It should be apparent that many of our habits and rituals are learned through unconscious conditioning. Habits can be efficient responses to frequently occurring situations. However, habits can be maladaptive as well, as occurs in addiction or obsessive–compulsive disorder.

FIGURE 30.7 Modern example of a Skinner box. This apparatus is the most widely used method for studying operant conditioning.

Forgetting

Some years ago, a poll showed that 84% of psychologists agreed with the statement "Everything we learn is permanently stored in the mind, although sometimes particular details are not accessible." The 16% who thought otherwise, however, were correct. Common sense indicates that,

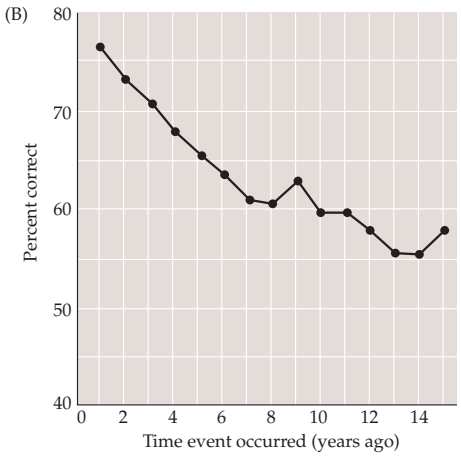


FIGURE 30.8 Forgetting. (A) Different versions of the "heads" side of a penny. Despite innumerable exposures to this familiar design, few people are able to select (a) as the authentic version. Clearly, repeated information is not necessarily retained. (B) The deterioration of long-term memories was evaluated in this example by a multiple-choice test in which the subjects were asked to recognize the names of television programs that had been broadcast for only one season during the past 15 years. Forgetting of stored information that is no longer used evidently occurs gradually and progressively over the years (chance performance = 25%). (A after Rubin and Kontis, 1983; B after Squire, 1989.)

were it not for forgetting, our brains would be impossibly burdened with the welter of useless information that is briefly encoded in our immediate, short-term and even long term memories. In fact, the human brain is very good at forgetting. Like the unreliable performance on tests such as the one shown in Table 30.1, Figure 30.8 shows that our memory of the appearance of a penny (an icon seen thousands of times since childhood) is uncertain at best, and that people tend to gradually forget what they have encoded in long-term memory. Clearly, we forget things that have no particular importance, and unused or unrehearsed memories deteriorate over time.

The ability to forget unimportant information may be as critical for normal life as the ability to retain information that is significant. Evidence for this presumption is demonstrated in rare individuals who have difficulty with the normal erasure of information. The best-known case is a subject studied over several decades by the Russian psychologist Alexander Luria, who referred to the subject simply as "S." Luria's description of an early encounter gives some idea why S, then a newspaper reporter, was so interesting:

> *I gave S a series of words, then numbers, then letters, reading them to him slowly or presenting them in written form. He read or listened attentively and then repeated the material exactly as it had been presented. I increased the number of elements in each series, giving him as many as thirty, fifty, or even seventy words or numbers, but this too, presented no problem for him. He did not need to commit any of the material to memory; if I gave him a series of words or numbers, which I read slowly and distinctly, he would listen attentively, sometimes ask me to stop and enunciate a word more clearly, or, if in doubt whether he had heard a word correctly, would ask me to repeat it. Usually during an experiment he would close his eyes or stare into space, fixing his gaze on one point; when the experiment was over, he would ask that we pause while he went over the material in his mind to see if he had retained it. Thereupon, without another moment's pause, he would reproduce the series that had been read to him.*
>
> A. R. Luria (1987), *The Mind of a Mnemonist*, pp. 9–10

S's phenomenal memory did not always serve him well, however. He had difficulty ridding his mind of the trivial information that he tended to focus on, sometimes to the point of incapacitation. As Luria put it:

> *Thus, trying to understand a passage, to grasp the information it contains (which other people accomplish*

by singling out what is most important) became a tortuous procedure for S, a struggle against images that kept rising to the surface in his mind. Images, then, proved an obstacle as well as an aid to learning in that they prevented S from concentrating on what was essential. Moreover, since these images tended to jam together, producing still more images, he was carried so far adrift that he was forced to go back and rethink the entire passage. Consequently, a simple passage—a phrase, for that matter—would turn out to be a Sisyphean task.

Ibid., p. 113

Luria's patient presumably represents one extreme of a continuum. A number of otherwise normal individuals have what has come to be referred to as *superior autobiographical memory*, the best known of whom is the television actress Marilu Henner. Although not negatively afflicted like Luria's patient, these individuals remember far more details about their daily lives than most of us. Even if years in the past, Henner and others can apparently remember the day of the week pertinent to a given date and much of what occurred that day.

Amnesia

Although forgetting is a normal (and essential) process, it can also be pathological, a condition called **amnesia**. An inability to establish new memories following neurological insult is called **anterograde amnesia**, whereas difficulty retrieving memories established prior to the precipitating neuropathology is called **retrograde amnesia**. Anterograde and retrograde amnesia are often present together, but can be dissociated under various circumstances. Amnesias following bilateral lesions of the temporal lobe and diencephalon have given particular insight into where and how at least some categories of memory are formed and where they are stored, as discussed in the following section.

Brain Systems Underlying Declarative Memory Acquisition and Storage

Several extraordinary clinical cases of amnesia have been especially revealing about the neural systems responsible for the short-term storage and consolidation of declarative information (Clinical Applications). Taken together, these cases provide dramatic evidence of the importance

CLINICAL APPLICATIONS

Some Especially Instructive Clinical Cases

H. M.

Henry Molaison, known only as "H. M." while he was still alive, had suffered minor seizures since age 10 and major seizures since age 16. In 1953, at the age of 27, he underwent surgery to correct his increasingly debilitating epilepsy. A high school graduate, H. M. had been working as a technician in a small electrical business until shortly before the time of his operation. His attacks involved generalized convulsions with tongue biting, incontinence, and loss of consciousness (all typical of grand mal seizures). Despite a variety of medications, the seizures remained uncontrolled and increased in severity. A few weeks before his surgery, H. M. became unable to work and had to quit his job.

On September 1, 1953, surgeons performed a bilateral medial temporal lobe resection in which the amygdala, uncus, hippocampal gyrus, and anterior two-thirds of the hippocampus were removed (Figures A–D). At the time, it was unclear that bilateral surgery of this kind would cause a profound memory defect. Severe amnesia was evident, however, upon H. M.'s recovery from the operation; and although his epilepsy was well controlled, his life thereafter was radically changed.

The first formal psychological exam of H. M. was conducted nearly 2 years after the operation, at which time a profound memory defect was still obvious. Just before the examination, for instance, H. M. had been talking to the psychologist; yet he had no recollection of this experience a few minutes later, denying that anyone had spoken to him. He gave the date as March 1953 and seemed oblivious to the fact that he had undergone an operation, or that he had become incapacitated as a result. Nonetheless, his score on the Wechsler-Bellevue Intelligence Scale was 112, a value not significantly different from his preoperative IQ. Various psychological tests failed to reveal any deficiencies in perception, abstract thinking, or reasoning; he seemed highly motivated and, in the context of casual conversation, normal. Importantly, he also performed well on tests of the ability to learn new skills, such as mirror writing or puzzle solving (i.e., his ability to form nondeclarative memories was intact). Moreover, his early memories were easily recalled, showing that the structures removed during H. M.'s operation are not a permanent repository for such information. On the Wechsler Memory Scale (a specific test of declarative memory), however, he performed very poorly, and he could not recall a preceding test set once he had turned his attention to another part of the exam. These deficits, along with his obvious inability to recall events in his daily life, all indicated a profound loss of short-term declarative memory function.

H. M. was studied extensively during the subsequent decades, primarily by Brenda Milner and her colleagues at the Montreal Neurological Institute. His memory deficiency continued unabated, and according to Milner, he had little idea who she was in spite of their acquaintance for nearly 50 years. Sadly, he gradually came to appreciate his

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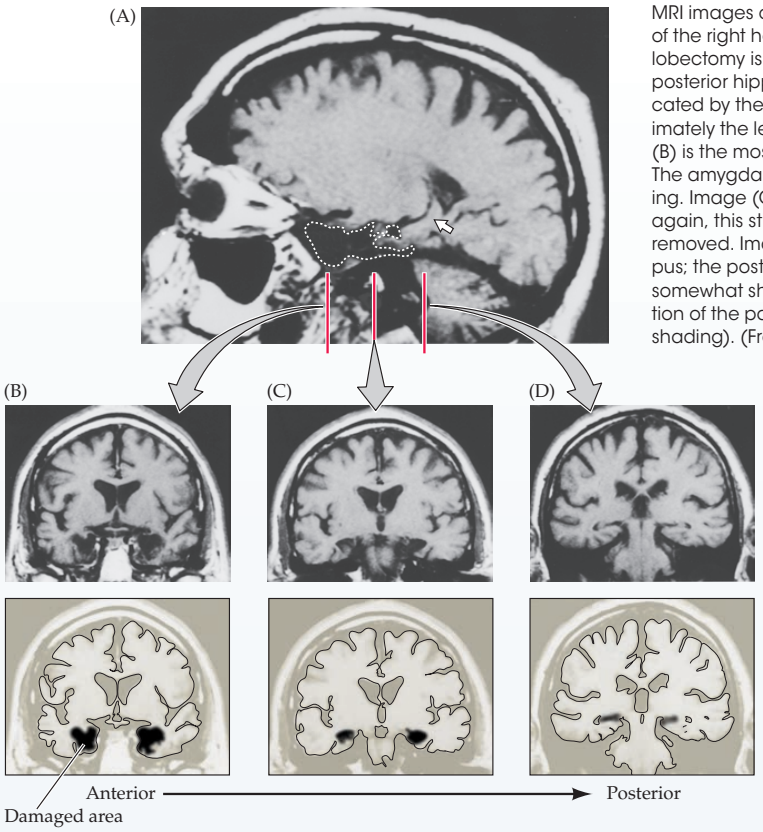
CLINICAL APPLICATIONS ■ (*continued*)



MRI images of the brain of patient H. M. (A) Sagittal view of the right hemisphere; the area of the anterior temporal lobectomy is indicated by the white dotted line. The intact posterior hippocampus is the banana-shaped object indicated by the white arrow. (B–D) Coronal sections at approximately the levels indicated by the red lines in (A). Image (B) is the most rostral and is at the level of the amygdala. The amygdala and the associated cortex are entirely missing. Image (C) is at the level of the rostral hippocampus; again, this structure and the associated cortex have been removed. Image (D) is at the caudal level of the hippocampus; the posterior hippocampus appears intact, although somewhat shrunken. Outlines below give a clearer indication of the parts of H. M.'s brain that were ablated (black shading). (From Corkin et al., 1997.)

predicament. "Every day is alone," H. M. reported, "whatever enjoyment I've had and whatever sorrow I've had." H. M. died in 2008 at age 82.

N. A.

N. A. was born in 1938 and grew up with his mother and stepfather, attending public schools in California. After a year of junior college, he joined the Air Force. In October of 1959 he was assigned to the Azores as a radar technician and remained there until December 1960, when a bizarre accident made him a celebrated neurological case.

N. A. was assembling a model airplane in his barracks room while, unbeknownst to him, his roommate was practicing thrusts and parries with a miniature fencing foil behind N. A.'s chair. N. A. turned suddenly and was stabbed through the right nostril. The foil penetrated the cribriform plate (the structure through which the olfactory nerve enters the brain) and took an upward course into the left forebrain. N. A. lost consciousness within a few minutes (presumably because of bleeding in the region of brain injury) and was taken to a hospital. There he exhibited right-side weakness and paralysis of the right eye muscles innervated by the third cranial nerve. Exploratory surgery was undertaken and the dural tear repaired. Gradually, he recovered and was sent home to California. After some months, his only general neurological deficits were some weakness of upward gaze and mild double vision. He retained, however, a severe anterograde amnesia for declarative memories. MRI studies first carried out in 1986 showed extensive damage to the thalamus and nearby tracts, mainly on the left side; there was also damage to the right anterior temporal lobe. The exact extent of his lesion, however, is not known, as N. A. remains alive and well.

N. A.'s memory from the time of his injury (more than 40 years ago) to the present has remained impaired, and like H. M., he fails badly on formal tests of new learning ability. His IQ is 124, and he shows no defects in language skills, perception, or other measures of intelligence. He also learns new nondeclarative skills quite normally. His amnesia is not as dense as that of H. M. and is more verbal than spatial. He can, for example, draw accurate diagrams of material presented to him earlier. Nonetheless, he loses track of his possessions, forgets what he has done, and tends to forget who has come to visit him. He has only vague impressions of political, social, and sporting events that have occurred since his injury. When watching television, he tends to forget the story line during commercials. However, his memory for events prior to 1960 is extremely good; indeed, his lifestyle tends to reflect the 1950s.

R. B.

At the age of 52, R. B. suffered an ischemic episode during cardiac bypass surgery. Following recovery from anesthesia, a profound amnesic disorder was apparent. As in the cases of H. M. and N. A., R. B.'s IQ was normal (111) and he showed no evidence of cognitive defects other than memory impairment. R. B. was tested extensively for the next 5 years, and while his amnesia was not as severe as that of H. M. or N. A., he consistently failed the standard tests of the

CLINICAL APPLICATIONS (*continued*)

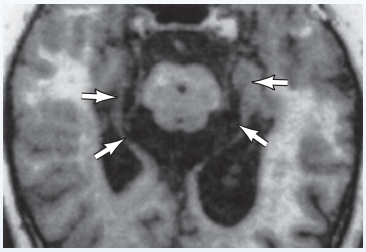
ability to establish new declarative memories. When R. B. died of congestive heart failure in 1983, a detailed examination of his brain was carried out. The only significant finding was bilateral lesions of the hippocampus—specifically, cell loss in the CA1 region that extended the full rostral–caudal length of the hippocampus on both sides. The amygdala, thalamus, and mammillary bodies, as well as the structures of the basal forebrain, were normal. R. B.'s case is particularly important because it suggests that hippocampal lesions alone can result in profound anterograde amnesia for declarative memory.

K. C.

As a young man, K. C. had a motorcycle accident in which he sustained damage to several brain regions, including the hippocampus (Figure E). As with the other patients described here, K. C.'s intellectual abilities were well preserved; he is able to read, write, and play chess at much the same level as before his accident (Figure F). However, both his anterograde and retrograde episodic memory are severely impaired.

Unlike H. M.'s amnesia, K. C.'s retrograde amnesia covers his whole life and he can remember little, if any, personal history. Nonetheless, his memory for semantic information acquired before the accident is intact. He has a good vocabulary, and his knowledge of subjects such as mathematics, history, and geography is not greatly different from that of others with his educational background. K. C.'s case thus exemplifies how extensive medial temporal lobe damage can, in at least some cases, impair retrograde *episodic* memory while sparing retrograde *semantic* memory. It could be that K. C.'s general knowledge was acquired earlier than the episodic memories tested and hence was more consolidated and less dependent on the hippocampus and surrounding structures. However, he can readily retrieve semantic information (e.g., the meaning of highly technical terms) he acquired while working as a machinist, whereas he fails to remember events that occurred in the factory during the same time period.

(E)



(F)

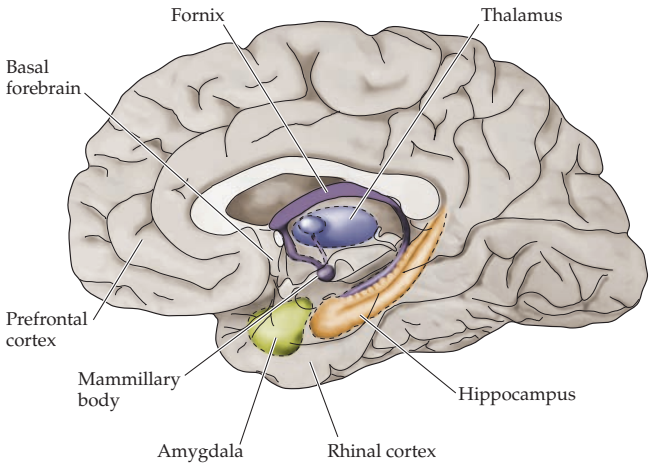
(E) An MRI image shows patient K. C.'s bilateral hippocampal and parahippocampal damage (arrows). (F) Although he has severe episodic amnesia, K. C.'s semantic memories remain largely intact. (E from Rosenbaum et al., 2000; F from Tulving, 2002.)

of midline diencephalic and medial temporal lobe structures—the hippocampus, in particular—in establishing new declarative memories (Figure 30.9). These patients also demonstrate that there is a different anatomical substrate for anterograde and retrograde amnesia, since memories for events and other information acquired before the brain damage they suffered was largely retained. Thus, this sort of injury produces primarily anterograde amnesia.

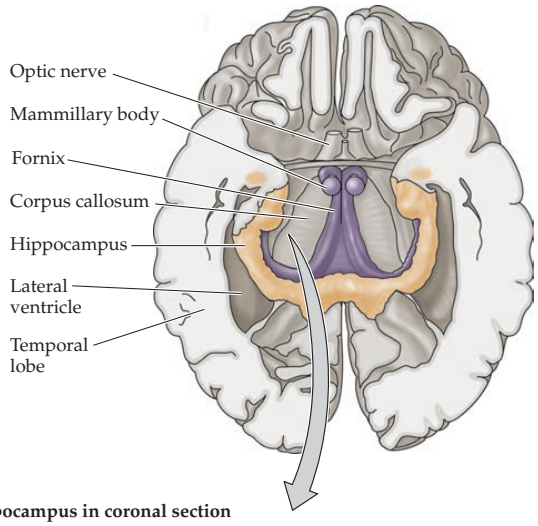
Studies of animals with lesions of the medial temporal lobe have largely corroborated these findings in human patients. For example, one test of the presumed equivalent of declarative memory formation in animals involves placing rats into a pool filled with opaque water, thus concealing a submerged platform. Surrounding the pool are prominent visual landmarks (Figure 30.10). Normal rats at first search randomly until they find the submerged platform. After repeated testing, however, they learn to swim directly to the platform no matter where they are initially placed in the pool by orienting to the landmarks. Rats with lesions of the hippocampus and nearby structures cannot learn to find the platform, suggesting that remembering its location relative to visual landmarks depends on the same neural structures critical to declarative memory formation in humans. Likewise, destruction of the hippocampus and parahippocampal gyrus in monkeys severely impairs their ability to perform delayed response tasks. These studies suggest that primates and other mammals depend on medial temporal structures to encode and initiate the consolidation of memories of events, just as humans use these same brain regions for the initial encoding and consolidation of declarative memories.

Consistent with the evidence from studies of humans and other animals with lesions to the medial temporal lobe—in particular, to the hippocampus and parahippocampal cortex—recent studies have shown that neurons in these areas are selectively recruited by tasks that involve declarative memory. For example, neuroimaging studies using positron emission tomography show increased metabolism in the hippocampus of human subjects studying information they would later be asked to recall. Studies using fMRI have also shown that the hippocampus and parahippocampal gyrus are activated in human subjects studying a list of items to be remembered. Moreover the

(A) **Brain areas associated with declarative memory disorders**



(B) **Ventral view of hippocampus and related structures with part of temporal lobes removed**



(C) **Hippocampus in coronal section**

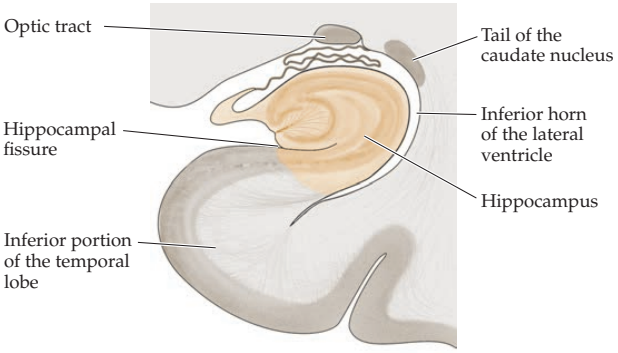


FIGURE 30.9 Brain areas that support declarative memory. By inference from the results of damage to these structures, declarative memory is based on their physiological activity. (A) Studies of amnesic patients have shown that the formation of declarative memories depends on the integrity of the hippocampus and its subcortical connections to the mammillary bodies and dorsal thalamus. (B) Location of the hippocampus as seen in a cutaway view in the horizontal plane. (C) The hippocampus as it would appear in a histological section in the coronal plane, at approximately the level indicated by the line in (B).

amount of activity measured in these areas was higher for items that subjects subsequently remembered compared with the activity measured for items they later forgot (Figure 30.11).

Another example of the importance of medial temporal lobe structures in the formation and consolidation of declarative memories is cab drivers. Anyone who has ridden a taxi in a large city can appreciate the difficulty of negotiating the labyrinth of streets to arrive at a specified destination. A much discussed study showed that the posterior hippocampus, which appears to be particularly useful in remembering spatial information, is larger in London taxi drivers than in age-matched control subjects (Figure 30.12A). Confirming the role of experience in performance, the size of the posterior hippocampus in cab drivers scales positively with the number of months spent driving a cab (Figure 30.12B). Together, such findings support the idea that neuronal activation within the hippocampus and closely allied cortical areas of the medial temporal lobe largely determines the transfer of declarative information into long-term memory, and that the robustness with which such memories are encoded depends on structural and functional changes of neural connections that occur as a result of experience.

In contrast, retrograde amnesia—the loss of memory for events preceding an injury or illness—is more typical of the generalized lesions associated with head trauma and neurodegenerative disorders, such as Alzheimer's disease (Box 30C). Although a degree of retrograde amnesia can occur with the more focal lesions that cause anterograde amnesia, the long-term storage of memories is presumably distributed throughout the brain (see the following sections). Thus, the hippocampus and related diencephalic structures indicated in Figure 30.9 are critical for the initial formation and consolidation of declarative memories that are ultimately stored elsewhere. Together, these observations have lead researchers to think of the hippocampus as providing a *cognitive map*, an idea that is consistent with studies in rodents (Box 30D).

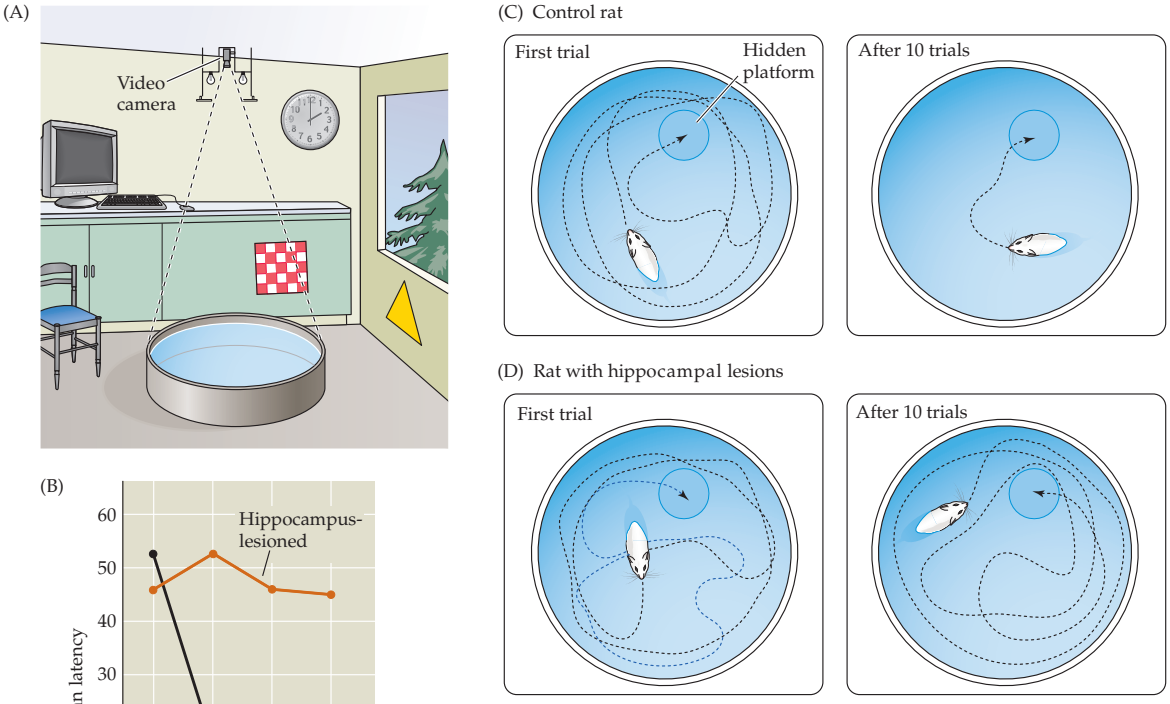


FIGURE 30.10 Spatial learning and memory in rodents depends on the hippocampus. (A) Rats are placed in a circular tank about the size and shape of a child's wading pool, filled with opaque (milky) water. The surrounding environment contains visual cues such as windows, doors, a clock, and so on. A small platform is located just below the surface. As rats search for this resting place, the pattern of their swimming (indicated by the traces in C and D) is monitored by a video camera. (B) After a few trials, normal rats rapidly reduce the time required to find the platform, whereas rats with hippocampal lesions do not. Sample swim paths of normal (C) and hippocampus-lesioned (D) rats on the first and tenth trials. Rats with hippocampal lesions are unable to remember where the platform is located. (B after Eichenbaum, 2000; C,D after Schenk and Morris, 1985.)

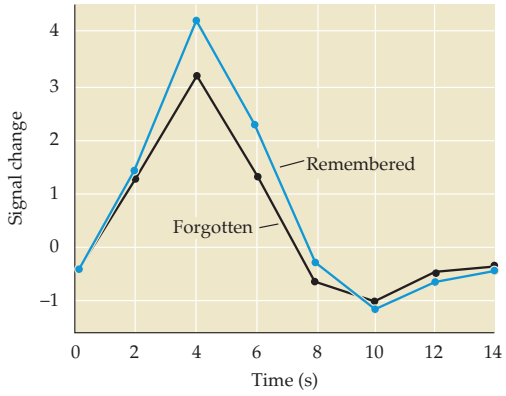


FIGURE 30.11 Activation of the hippocampus and adjacent parahippocampal cortex predicts memory performance. Activation in these areas was much stronger for items that were later remembered. (After Wagner et al., 1998.)

Sites of Long-Term Memory Storage

Revealing though they have been, clinical studies of amnesic patients have provided relatively little insight into the long-term storage of declarative information in the brain, other than to indicate that such information is *not* stored in the midline diencephalic and medial temporal lobe structures that are affected in anterograde amnesia. A good deal of evidence accumulated over the years implies that the cerebral cortex is the major long-term repository for many aspects of declarative memory.

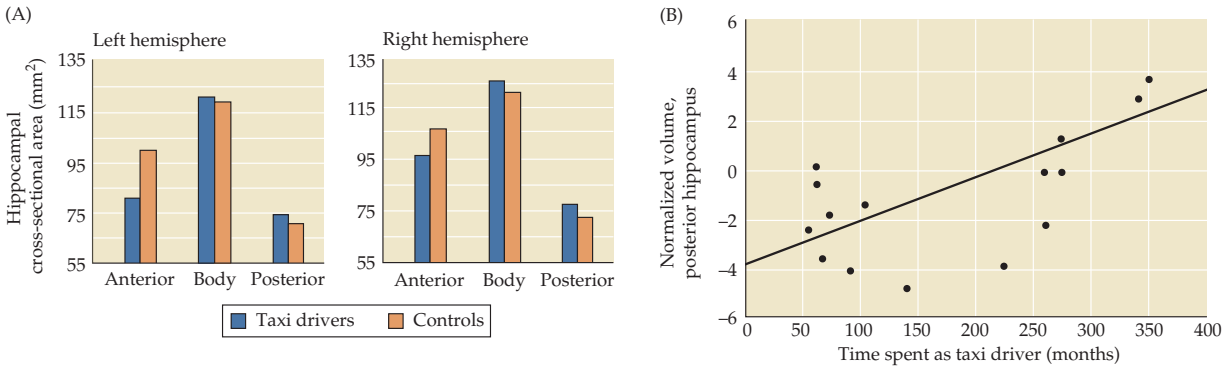


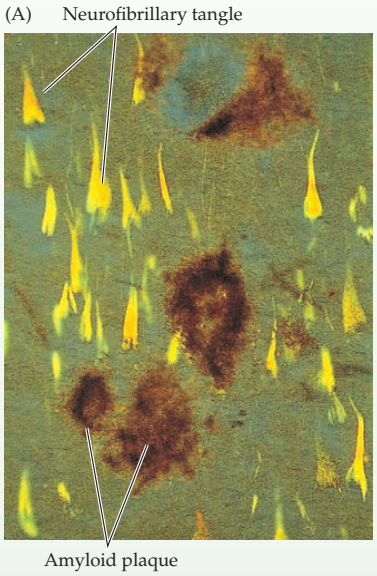
FIGURE 30.12 The hippocampus in London taxi drivers. (A) Structural brain scans show that the posterior hippocampus, a region specialized for remembering spatial information, is larger in taxi drivers than in age-matched controls. (B) Hippocampus size scales positively with experience as a cabbie. (After Maguire et al., 2000.)

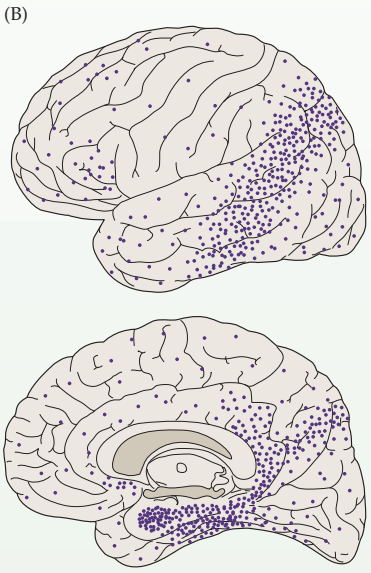
BOX 30C ■ Alzheimer's Disease

Dementia is a syndrome characterized by failure of recent memory and other intellectual functions. It is usually insidious in onset but tends to progress steadily. Alzheimer's disease (AD) is the most common dementia, accounting for 60% to 80% of cases in the elderly. This unfortunate condition afflicts 5% to 10% of the U.S. population over the age of 65 and as much as 45% of the population over 85. The earliest signs are an impairment of recent memory function and attention, followed by failure of language skills, visual–spatial orientation, abstract thinking, and judgment. Alterations of personality inevitably accompany these defects.

A tentative diagnosis of AD is based on these characteristic clinical features and can be confirmed only by the distinctive cellular pathology evident on post mortem examination of the brain (Figure A). These histopathological changes consist of three principal features: (1) collections of intraneuronal cytoskeletal filaments called *neurofibrillary tangles*; (2) extracellular deposits of an abnormal protein (called amyloid) in so-called *senile plaques*; and (3) a diffuse loss of neurons. These changes are most apparent in neocortex, limbic structures (hippocampus, amygdala, and their associated cortices), and some brainstem nuclei (typically, the basal forebrain nuclei) (Figure B).

The vast majority of AD cases are "late-onset," arising after age 60 without an obvious cause. In contrast, relatively rare early-onset forms appear in middle life and are caused by monogenic defects consistent with an autosomal dominant pattern of inheritance. Identification of the mutant genes in a few families with the early-onset form has provided considerable insight into the processes that go awry in AD.





(A) Histological section of the cerebral cortex from a patient with Alzheimer's disease, showing characteristic amyloid plaques and neurofibrillary tangles. (B) Distribution of pathologic changes (including plaques, tangles, neuronal loss, and gray matter shrinkage) in Alzheimer's disease. Dot density indicates severity of pathology. (A courtesy of Gary W. Van Hoesen; B after Blumenfeld, 2002, based on Brun and Englund, 1981.)

BOX 30C ■ (*continued*)

Investigators long suspected that a mutant gene responsible for familial AD might reside on chromosome 21, primarily because clinical and neuropathologic features similar to AD often occur in individuals with Down syndrome (caused by an extra copy of chromosome 21), but with a much earlier onset (about age 30, in most cases). A mutation of the gene encoding amyloid precursor protein (APP) emerged as an attractive candidate both because of the prominent amyloid deposits in AD together with isolation of a fragment of APP, Aβ peptide, from amyloid plaques. The gene that encodes APP was subsequently cloned by Dmitry Goldgaber and his colleagues and found to reside on chromosome 21. This discovery eventually led to the identification of mutations of the *APP* gene in almost 20 families with the early-onset, autosomal dominant form of AD. It should be noted, however, that only a few of the early-onset families (and none of the late-onset families) exhibited these particular mutations.

The mutant genes underlying two additional autosomal dominant forms of AD have been subsequently identified as *presenilin 1* and *presenilin 2*. Mutations of these two genes modify processing of APP and result in increased amounts of a particularly toxic form of Aβ peptide, Aβ42. Thus, mutation of any one of several genes appears to be sufficient to cause a heritable form of AD, and these converge on abnormal processing of APP.

In the far more common late-onset form of AD, the disease is clearly not inherited in any simple sense (although the relatives of affected individuals are at a greater risk, for reasons that are not clear). The central role of APP in the families with early-onset forms of the disease nonetheless suggested that APP might be linked to the chain of events culminating in the sporadic forms of AD. Biochemists Warren Strittmatter and Guy Salvesen theorized that pathologic deposition of proteins complexed with Aβ peptide might be responsible.

To test this idea, Strittmatter and Salvesen immobilized Aβ peptide on nitrocellulose paper and searched for proteins in the cerebrospinal fluid of patients with AD that bound with high affinity. One of the proteins they detected was apolipoprotein E (ApoE), a molecule that normally chaperones cholesterol through the bloodstream. This discovery was especially provocative in light of another discovery, this one made by Margaret Pericak-Vance, Allen Roses, and their colleagues, who found that affected members of some families with the late-onset form of AD exhibited an association with genetic markers on chromosome 19. This finding was of particular interest because a gene encoding an isoform of ApoE is located in the same region of chromosome 19 implicated by the association studies. As a result, these researchers began to explore the relationship of the different alleles of *ApoE* with individuals with a sporadic, late-onset form of AD.

There are three major alleles of *ApoE*: *e2*, *e3*, and *e4*. The frequency of allele *e3* in the general population is 0.78, and the frequency of allele *e4* is 0.14. The frequency of the *e4* allele in late-onset AD patients, however, is 0.52—almost four times higher than in the general population. Thus, the inheritance of the *e4* allele is a risk factor for late-onset AD. In fact, people homozygous for *e4* are about eight times more likely to develop AD compared with individuals homozygous for *e3*. Among individuals with no copies of *e4*, only 20% develop AD by age 75, compared with 90% of individuals with two copies of *e4*.

In contrast to the mutations of *APP* or *presenilin 1* and *presenilin 2* that cause early-onset familial forms of AD, inheriting the *e4* form of ApoE is not sufficient to cause AD; rather, inheriting this gene simply increases the risk of developing AD. The cellular and molecular mechanisms by which the *e4* allele of ApoE increases susceptibility to late-onset AD are not understood, and elucidating these mechanisms is clearly an important goal.

Clearly, AD has a complex pathology and probably reflects a variety of related molecular and cellular abnormalities. So far, the most apparent common denominator seen in this complex disease is abnormal APP processing. In particular, accumulation of the toxic Aβ42 peptide is thought to be a key factor. This conclusion has led to efforts to develop therapies aimed at inhibiting formation or facilitating clearance of this toxic peptide. It is unlikely that this important problem will be understood without a great deal more research, the hyperbole in the lay press notwithstanding.

BOX 30D ■ Place Cells and Grid Cells

Nearly 70 years ago psychologist Edward Tolman suggested that the brain must possess a cognitive map that represents remembered places in the environment. In 2014 the Nobel Prize in Physiology or Medicine was awarded to three neurophysiologists (John O'Keefe, May-Britt Moser, and Edvard Moser) for their studies of navigation in rodents that confirmed Tolman's idea.

This work began in the late 1960s with O'Keefe's observation that some neurons in the rat hippocampus fire robustly when and only when freely moving animals in an arena occupy a specific place (Figure A). Based on a series of studies by O'Keefe and his colleagues, it became clear that the activity of different combinations of these *place cells* constituted the sort of learned cognitive map that Tolman had imagined. Although recording from neurons in behaving animals is now widely practiced, O'Keefe's group was one of the pioneers in this methodology.

The Mosers (husband and wife) added to this understanding of animal navigation by further exploring the activity of neurons in the entorhinal cortex, a region adjacent to the hippocampus and whose neurons project to it. They found that cells in this area also code for place, but other neurons they named grid cells showed quite different patterns of activity. Remarkably, each of these grid cells fired when the rat was in

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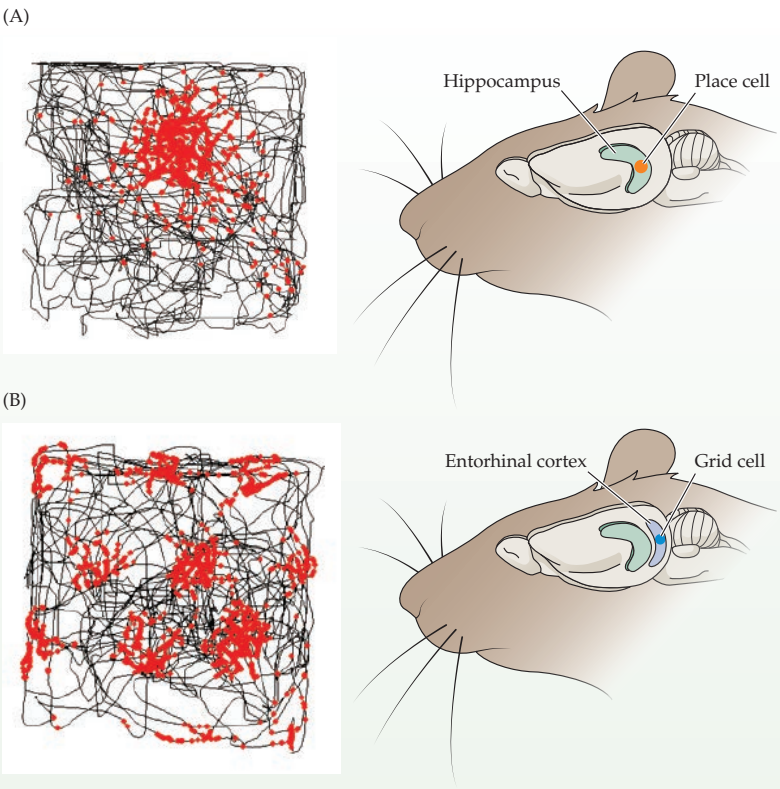
BOX 30D ■ (*continued*)



(A) Hippocampal place cells. The picture on the right shows the location of the hippocampus in a rat brain; the panel on the left illustrates place cells (orange dots) that fire only when the rat traverses a specific locus as it moves in an arena. (B) Entorhinal grid cells. The picture on the right shows the location of the entorhinal cortex adjacent to the hippocampus; the panel on the left represents the activity of a single grid cell as the rat traverses points in the arena that form a hexagonal grid (From Moser et al., 2008.).

multiple loci that formed a hexagonal grid (Figure B), thus mapping every point in the arena over distances ranging from centimeters to a few meters. The implied significance of *grid cells* is providing measurements of the arena which place cells in the hippocampus then use to couple environmental cues with distance and direction.

Although the link from these findings in rats and mice to human hippocampal and entorhinal functions remains largely speculative, it is not difficult to see how the learning deficits seen in H. M. and other patients with medial temporal lobe damage are related to these basic studies. Indeed, recordings from hippocampal neurons in patients undergoing surgery to relieve intractable epilepsy support this connection.

The idea that memory traces are distributed over the cortex began with the work of the American neuroscientist Karl Lashley in the 1920s. Lashley made cuts that disconnected various regions of the cortex in rats, performing this procedure either before or after the animals had learned to run mazes of varying difficulty. When the cuts he made failed to show much effect on the animals' memory of how to find the food reward in the maze, he went on to actually remove parts of the cortex (Figure 30.13A). Lashley found that the location of the lesions did not matter much—only the extent of the tissue destruction and the difficulty of the task seemed consequential (Figure 30.13B,C). He summarized his findings in terms of what he called the *mass action principle*, which states that any degradation in learning and memory depends on the amount of cortex destroyed; and that the more complex the learning task, the more disruptive the lesion. Only when the damage is widespread does network performance show a significant decline. These findings imply that, whereas acquiring declarative memories depends on the integrity of the medial temporal lobes, storing them over the long term depends on distributed cortical networks that are seriously impaired only when large portions of them are destroyed.

A second line of evidence supporting this interpretation comes from patients with severe depression who undergo electroconvulsive therapy (ECT). The passage of enough electrical current through the brain causes the equivalent of a full-blown seizure. This remarkably useful treatment (which is performed under anesthesia in well-controlled circumstances) was discovered because depression in epileptics often remitted after a spontaneous seizure. However, ECT often causes both anterograde and retrograde amnesia. Patients typically do not remember the treatment itself or the events of the preceding days, and their recall of events over the previous 1 to 3 years can be affected. Animal studies (e.g., rats tested for maze learning) have confirmed the amnesic consequences of ECT. To mitigate this side effect (which may be the result of excitotoxicity and tends to resolve over a few months), ECT is often delivered to only one hemisphere at a time. The nature

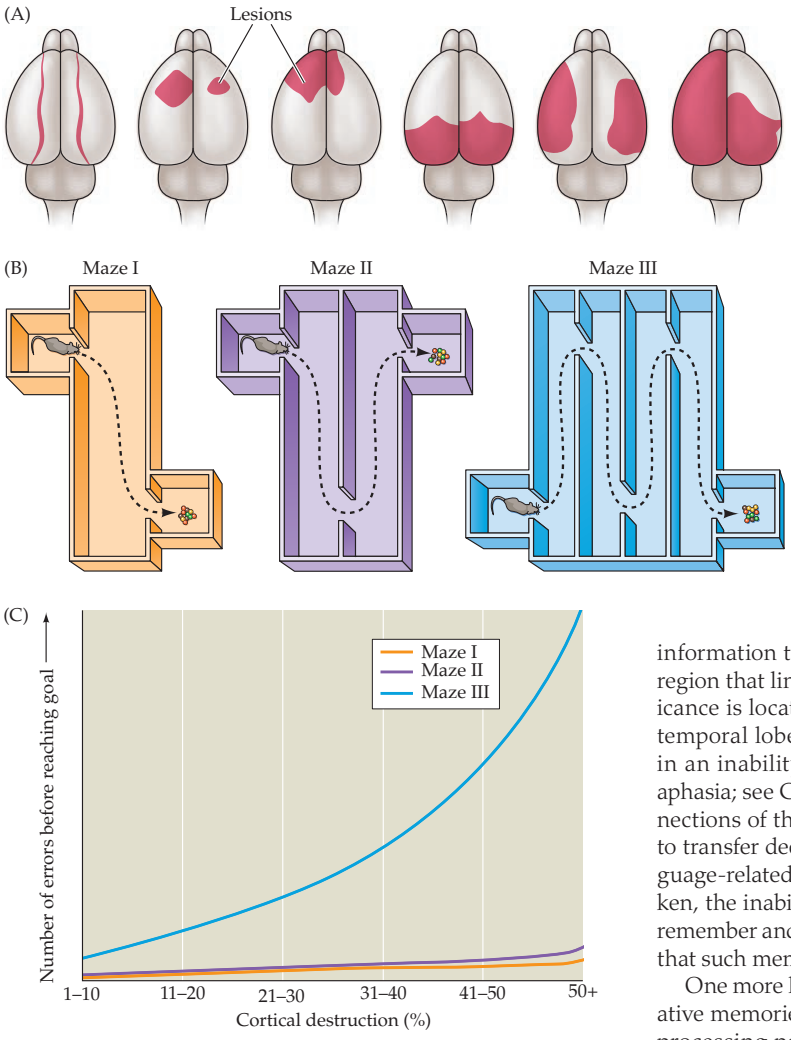


FIGURE 30.13 Lashley's experiments in search of the engram. (A) Lesions of varying size and location (red) were made in rat brains either before or after the animals had learned to run mazes (B) of varying complexity. (C) The reduction in learning Lashley observed was proportional to the amount of tissue destroyed; the lesion locations appear inconsequential. The more complex the learning task, however, the more the lesions affected performance. (After Lashley and Wiley, 1933; Lashley, 1944; and the University of Rome Psychology Lab Website.)

of amnesia following ECT supports the conclusion that long-term declarative memories are widely stored in the cerebral cortex.

Another sort of evidence comes from patients with damage to regions of the association cortex. Since different cortical regions have significantly different if overlapping functions (see Chapter 27), it is not surprising that these sites store information that reflects their function. For example, the region that links speech sounds and their symbolic significance is located in the association cortex of the superior temporal lobe, and damage to this area typically results in an inability to link words and meanings (Wernicke's aphasia; see Chapter 33). Presumably, the widespread connections of the hippocampus to the language areas serve to transfer declarative information to these and other language-related cortical sites (Figure 30.14). By the same token, the inability of patients with temporal lobe lesions to remember and thus recognize objects and/or faces suggests that such memories are stored in these cortical sites.

One more line of support for the hypothesis that declarative memories are stored in cortical areas specialized for processing particular types of information comes from neuroimaging of human subjects during the recollection of vivid memories. In one such study, subjects first examined

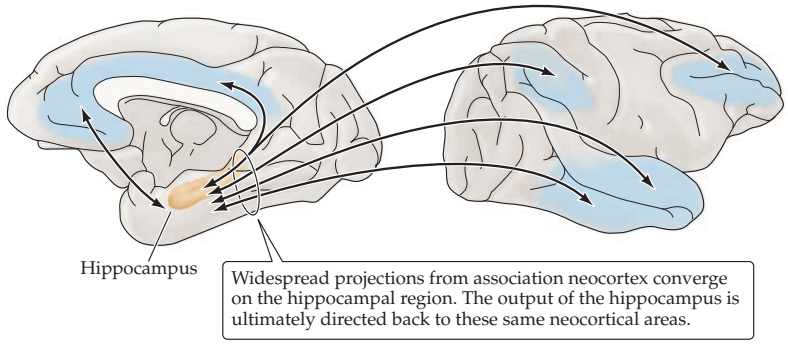


FIGURE 30.14 The hippocampus and possible declarative memory storage sites. The rhesus monkey brain is shown because these connections are much better documented in non-human primates than in humans. Projections from numerous cortical areas converge on the hippocampus and the related structures known to be involved in human memory; most of these sites also send projections to the same cortical areas. Medial and lateral views are shown, the latter rotated 180° for clarity. (After Van Hoesen, 1982.)

words paired with either pictures or sounds. Their brains were then scanned while they were asked to recall whether each test word was associated with either a picture or a sound. Functional images based on these scans showed that the cortical areas activated when subjects viewed pictures or heard sounds were reactivated when these percepts were vividly recalled. In fact, this sort of reactivation can be quite specific. Thus, different classes of visual images—for example, faces, houses, or chairs—tend to reactivate the same regions of the visual association cortex that were activated when the objects were actually perceived (Figure 30.15).

Finally, whereas the ability of patients such as H. M. (see Clinical Applications) to remember facts and events from the period of their lives preceding their lesions demonstrates that the medial temporal lobe is not necessary for retrieving declarative information held in long-term memory, other studies suggest that these structures may be important for recalling declarative memories during the early stages of consolidation and storage in the cerebral cortex.

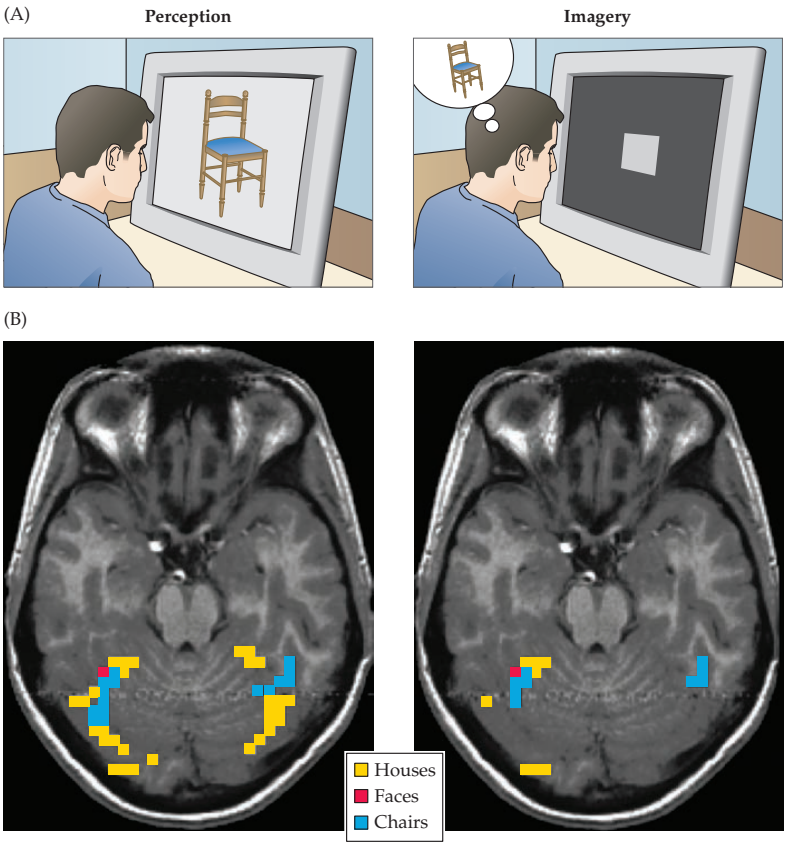


FIGURE 30.15 Reactivation of visual cortex during vivid remembering of visual images. (A) Subjects were instructed either to view images of houses, faces, and chairs (left) or to imagine the objects in the absence of the stimulus (right). (B) At left, bilateral regions of ventral temporal cortex are specifically activated during perception of houses (yellow), faces (red), and chairs (blue). At right, when subjects recall these objects, the same regions preferentially activated during the perception of each object class are reactivated. (From Buckner and Wheeler, 2001.)

Brain Systems Underlying Nondeclarative Memory Acquisition and Storage

The fact that patients such as H. M., N. A., and R. B. (see Clinical Applications) had no difficulty establishing or recalling nondeclarative memories implies that such information is laid down using a different anatomical substrate from that used in declarative memory formation. Nondeclarative memory apparently involves the basal ganglia, prefrontal cortex, amygdala, sensory association cortices, and cerebellum—but not the medial temporal lobe or midline diencephalon. In support of this view, perceptual priming (the unconscious influence of previously studied information on subsequent performance; see above) depends critically on the integrity of sensory association cortex. For example, lesions of the visual association cortex produce profound impairments in visual priming but leave declarative memory formation intact. Likewise, simple sensorimotor conditioning, such as learning to blink following a tone that predicts a puff of air directed at the eye, relies on the normal activation of neural circuits in the cerebellum. Ischemic damage to the cerebellum following infarcts of the superior cerebellar artery or the posterior inferior cerebellar artery causes profound deficits in classical eye-blink conditioning but does not interfere with the ability to lay down new declarative memories. Evidence from such *double dissociations* endorses the idea that relatively independent brain systems govern the formation and storage of declarative and nondecla-rative memories.

The connections between the basal ganglia and prefrontal cortex appear to be especially important for complex motor learning (see Chapter 18). Damage to either structure interferes with the ability to learn new motor skills. Patients

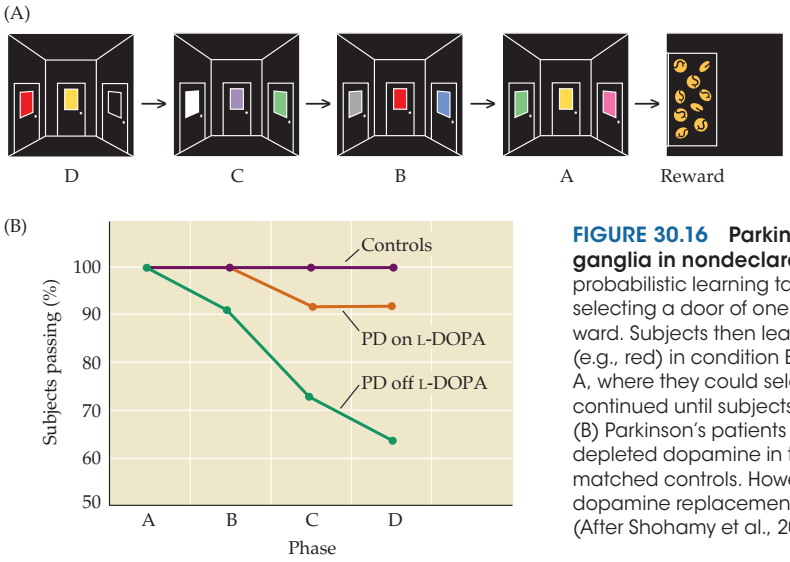


FIGURE 30.16 Parkinson's disease reveals a role for basal ganglia in nondeclarative memory. (A) Subjects performed a probabilistic learning task that had four levels. They first learned that selecting a door of one color (e.g., pink) in condition A led to a reward. Subjects then learned that selecting a differently colored door (e.g., red) in condition B would permit them to proceed to condition A, where they could select the rewarded door. This procedure was continued until subjects made choices from D → C → B → A → reward. (B) Parkinson's patients (PD) who were taking medication to replace depleted dopamine in the midbrain performed nearly as well as age-matched controls. However, Parkinson's patients who were not on dopamine replacement were impaired in their ability to learn the task. (After Shohamy et al., 2005.)

with Huntington's disease, which causes atrophy of the caudate and putamen, perform poorly on motor skill learning tests such as manually tracking a spot of light, tracing curves using a mirror, or reproducing sequences of finger movements. Because the loss of dopaminergic neurons in the substantia nigra interferes with normal signaling in the basal ganglia, patients with Parkinson's disease show similar deficits in motor skill learning (Figure 30.16), as do patients with prefrontal lesions caused by tumors or strokes. Neuroimaging studies have largely corroborated these findings, revealing activation of the basal ganglia and prefrontal cortex in normal subjects performing these same skill-learning tests. Activation of the basal ganglia and prefrontal cortex has also been observed in animals carrying out rudimentary motor learning and sequencing tasks.

The dissociation of memory systems supporting declarative and nondeclarative memory suggests the scheme for long-term information storage diagrammed in Figure 30.17. The generality of the diagram emphasizes the rudimentary state of present thinking about exactly how and where long-term memories are stored. A reasonable guess is that each complex memory is embodied in an extensive network of neurons whose activity depends on synaptic weightings that have been molded and modified by previous experience.

In sum, a variety of evidence indicates that long-term memories, whether declarative or nondeclarative, are stored throughout the brain. This conclusion, however, does not imply that individual memory traces are randomly distributed over the cortex. The current view is that memories are stored primarily within the brain regions originally involved in processing each kind of information. That is, the striate and extrastriate visual cortices store memory traces for visual information, auditory cortices store memory traces for auditory information, and so on. Moreover, some brain-damaged patients are impaired in very specific semantic or object categories, such as information about animals, and some forms of memory storage have been associated with memory mechanisms in restricted brain regions, such as the localization of eye-blink conditioning in the cerebellum, or fear conditioning in the amygdala.

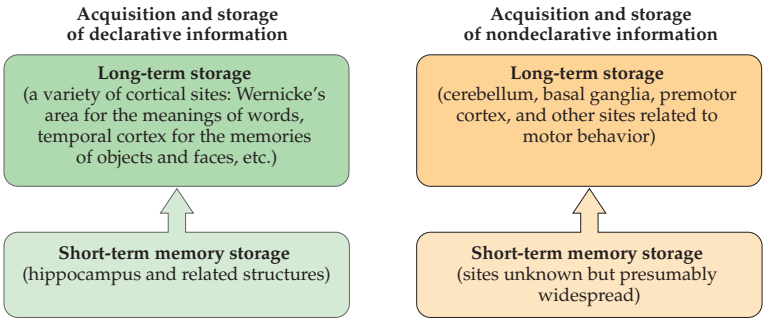


FIGURE 30.17 Summary diagram of the acquisition and storage of declarative versus nondeclarative information.

Memory and Aging

Although it is all too obvious that our outward appearance changes with age, most of us would like to believe that the brain is more resistant to the ravages of time. Unfortunately, the evidence suggests that this optimistic view is not justified. The average weight of the normal human brain determined at autopsy steadily decreases from early adulthood onward (Figure 30.18). In elderly individuals, this effect can also be observed with noninvasive imaging as a slight but nonetheless significant shrinkage of the brain. Counts of synapses in the cerebral cortex generally decrease in old age (although the number of neurons probably does not change very much), suggesting that it is mainly the connections between neurons that are lost as humans grow old, consistent with the idea that the networks of connections that represent memories—the engrams—gradually deteriorate.

These observations accord with the difficulty older people have in making associations (e.g., remembering names, or the details of recent experiences) and with declining scores on tests of memory as a function of age. The normal loss of some memory function with age means that clinicians must deal with a large "gray area" in distinguishing individuals subject to normal aging from those suffering from Alzheimer's disease (see Box 30C).

Just as regular exercise slows the deterioration of the neuromuscular system with age, age-related neurodegeneration and the associated cognitive decline may be slowed in elderly individuals who make a special effort to continue using the full range of both declarative and nondeclarative memory. Although cognitive decline with age is ultimately inevitable, neuroimaging studies suggest that high-performing older adults may to some degree offset declines in processing efficacy (Figure 30.19).

The inevitable loss of some memory ability in old age raises an ethical issue that most readers will be aware of. Many commercial offerings today advertise that their "brain exercises" will forestall or reverse this effect of aging, often with statements to the effect that the promised results are backed by "neuroscientific evidence." Such claims are true in the sense that any form or physical or mental exercise is beneficial in remaining as healthy as possible as the years pass, as physicians have long known. Whether these products are any better than the mental activity that comes from any interest, hobby, or other form of mental engagement is at best unproven.

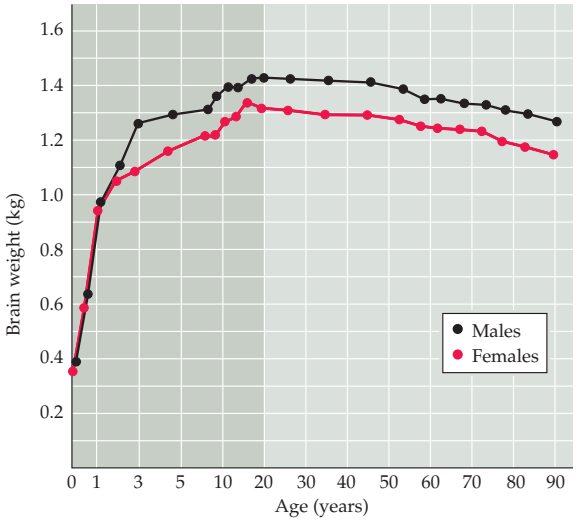


FIGURE 30.18 Brain size as a function of age. The human brain reaches its maximum size (measured by weight in this case) in early adult life and decreases progressively thereafter. This decrease evidently represents the gradual loss of neural circuitry in the aging brain, which presumably underlies the progressively diminished memory function in older individuals. (After Dekaban and Sadowsky, 1978.)

Summary

Human memory entails many biological strategies and anatomical substrates. Primary among these are a system for memories that can be expressed by means of language and can be made available to the conscious mind (declarative memory) versus systems that concern skills and associations that are essentially nonverbal, operating at a largely

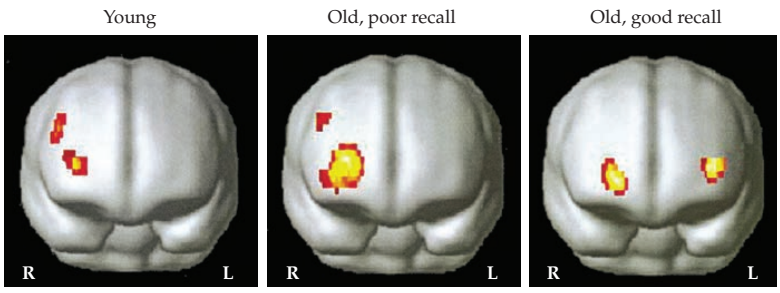


FIGURE 30.19 Compensatory activation of memory areas in high-functioning older adults. During remembering, activity in prefrontal cortex was restricted to the right prefrontal cortex (following radiological conventions, the brain images are left–right reversed) in both young participants and elderly subjects with poor recall. In contrast, elderly subjects with relatively good memory showed activation in both right and left prefrontal cortex. (After Cabeza et al., 2002.)

unconscious level (nondeclarative or procedural memory). Based on evidence from amnesic patients and knowledge about normal patterns of neural connections in the human brain, the hippocampus and associated midline diencephalic and medial temporal lobe structures are critically important in acquiring and consolidating declarative memories, although not in storing them, which occurs primarily in the cerebral cortices. In contrast, the acquisition and consolidation of nondeclarative memories for motor and other unconscious skills depend on the integrity of the premotor cortex, basal ganglia, and cerebellum, and are not affected by lesions that impair the declarative memory system. The common denominator of stored information is generally thought to be alterations in the strength and number of the synaptic connections in the cerebral cortices that mediate associations between stimuli and the behavioral responses to them, which include perceptions, thoughts, and emotions as well as motor actions.

ADDITIONAL READING

Reviews

Buckner, R. L. (2000) Neuroimaging of memory. In *The New Cognitive Neurosciences*, 2nd Edition, M. Gazzaniga (ed.). Cambridge, MA: MIT Press, pp. 817–840.

Buckner, R. L. (2002) The cognitive neuroscience of remembering. *Nature Rev. Neurosci.* 2: 624–634.

Cabeza, R. (2001) Functional neuroimaging of cognitive aging. In *Handbook of Functional Neuroimaging of Cognition*, R. Cabeza and A. Kingstone (eds.). Cambridge, MA: MIT Press, pp. 329–377.

Curtis, C. E. and M. D'Esposito (2006) Functional neuroimaging of working memory. In *Handbook of Functional Neuroimaging of Cognition*, 2nd Edition, R. Cabeza and A. Kingstone (eds.). Cambridge, MA: MIT Press, pp. 269–306.

Eichenbaum, H., A. R. Yonelinas and C. Ranganath (2007) The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* 30: 123–152.

Erickson, C. A., B. Jagadeesh and R. Desimone (2000) Learning and memory in the inferior temporal cortex of the macaque. In *The New Cognitive Neurosciences*, 2nd Edition, M. Gazzaniga (ed.). Cambridge, MA: MIT Press, pp. 743–752.

Gallistel, C. R. and L. D. Matzel (2013) The neuroscience of learning: Beyond the Hebbian synapse. *Annu. Rev. Psychol.* 64: 169–200. doi: 10.1146/anurev-psych-113011-143807

LeDoux J. E. (2007) Consolidation: Challenging the traditional view. In, H. L. Roediger, Y. Dudai. and S. M. Fitzpatrick (eds.) *Science of Memory: Concepts*. New York: Oxford University Press, pp. 171–175.

Mishkin, M. and T. Appenzeller (1987) The anatomy of memory. *Sci. Am.* 256: 80–89.

Poldrack, R. A. and D. T. Willingham (2006) Functional neuroimaging of skill learning. In *Handbook of Functional Neuroimaging of Cognition*, 2nd Edition, R. Cabeza and A. Kingstone (eds.). Cambridge, MA: MIT Press.

Schacter, D. L. and R. L. Buckner (1998) Priming and the brain. *Neuron* 20: 185–195.

Schiller, D. and 6 others (2015) Memory and Space: Towards an Understanding of the Cognitive Map. *J. Neurosci.* 35: 13904–13911.

Squire, L. R. and B. J. Knowlton (2000) The medial temporal lobe, the hippocampus, and the memory systems of the brain. In *The New Cognitive Neurosciences*, 2nd Edition, M. Gazzaniga (ed.). Cambridge, MA: MIT Press, pp. 765–779.

Squire, L. R., C. E. Stark And R. E. Clark (2004) The medial temporal lobe. *Annu. Rev. Neurosci.* 27: 279–306.

Thompson, R. F. (2005) In search of memory traces. *Annu. Rev. Psychol*. 56: 1–23.

Important Original Papers

Cabeza, R., N. D. Anderson, J. K. Locantore and A. R. McIntosh (2002) Aging gracefully: Compensatory brain activity in high-performing older adults. *NeuroImage* 17: 1394–1402.

Clark, R. E. And L. R. Squire (1998) Classical conditioning and brain systems: The role of awareness. *Science* 280: 77–81.

Gobet, F. and H. A. Simon (1998) Expert chess memory: Revisiting the chunking hypothesis. *Memory* 6: 225–255.

Ishai, A., L. G. Ungerleider and J. V. Haxby (2000) Distributed neural systems for the generation of visual images. *Neuron* 28: 979–990.

LaBar K. S. and R. Cabeza (2006) Cognitive neuroscience of emotional memory. *Nature Rev. Neurosci.* 7: 54–64. doi: 10.1038/nrn1825

Scoville, W. B. and B. Milner (1957) Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiat.* 20: 11–21.

Squire, L. R. (1989) On the course of forgetting in very long-term memory. *J. Exp. Psychol.* 15: 241–245.

Wheeler, M. A., D. T. Stuss and E. Tulving (1995) Frontal lobe damage produces episodic memory impairment. *J. Internatl. Neuropsychol. Soc.* 1: 525–536.

Zola-Morgan, S. M. and L. R. Squire (1990) The primate hippocampal formation: Evidence for a time-limited role in memory storage. *Science* 250: 288–290.

Books

Baddeley, A. (1982) *Your Memory: A User's Guide*. New York: Macmillan.

Craik, F. I. M. and T. A. Salthouse (eds.) (1999) *The Handbook of Aging and Cognition*. Mahwah, NJ: Lawrence Erlbaum Associates.

Eichenbaum, H. and N. J. Cohen (2001) *From Conditioning to Conscious Recollection: Memory Systems of the Brain.* New York: Oxford University Press.

Gazzaniga, M. S. (2000) *The New Cognitive Neurosciences*, 2nd Edition. Cambridge MA: MIT Press.

Gazzaniga, M. S., R. B. Ivry and G. R. Mangun (2008) *Cognitive Neuroscience: The Biology of the Mind*, 3rd Edition. New York: W. W. Norton & Company.

Luria, A. R. (1987) *The Mind of a Mnemonist* (translated by L. Solotaroff). Cambridge, MA: Harvard University Press.

Miyake, A. and P. Shah (2001) *Models of Working Memory.* Cambridge: Cambridge University Press.

Neisser, U. (1982) *Memory Observed: Remembering in Natural Contexts.* San Francisco: W. H. Freeman.

Purves, D. and 5 others (2013) *Principles of Cognitive Neuroscience*, 2nd Edition. Sunderland, MA: Sinauer Associates.

Saper, C. B. and F. Plum (1985) *Handbook of Clinical Neurology*, Vol. 1 (45): *Clinical Neuropsychology*, P. J. Vinken, G. S. Bruyn and H. L. Klawans (eds.). New York: Elsevier, pp. 107–128.

Schacter, D. L. (2001) *The Seven Sins of Memory: How the Mind Forgets and Remembers.* Boston: Houghton Mifflin Co.

Squire, L. R. And E. R. Kandel (2000) *Memory: From Mind to Molecules.* New York: Holt.