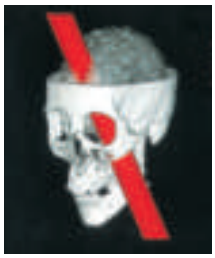
Chapter 30



Memory

Overview

One of the most intriguing of the brain's complex functions is the ability to store information provided by experience and to retrieve much of it at will. Without this ability, many of the cognitive functions discussed in the preceding chapters could not occur. *Learning* is the name given to the process by which new information is acquired by the nervous system and is observable through changes in behavior. *Memory* refers to the encoding, storage, and retrieval of learned information. Equally fascinating (and important) is the normal ability to forget information. Pathological forgetfulness, or amnesia, has been especially instructive about the neurological underpinnings of memory; amnesia is defined as the inability to learn new information or to retrieve information that has already been acquired. The importance of memory in daily life has made understanding these several phenomena one of the major challenges of modern neuroscience, a challenge that has only begun to be met. The mechanisms of plasticity that provide plausible cellular and molecular bases for some aspects of information storage have been considered in Chapters 22 through 24. The present chapter summarizes the broader organization of human memory, surveys the major clinical manifestations of memory disorders, and considers the implications of these disorders for ultimately understanding human memory in more detailed terms.

Qualitative Categories of Human Memory

Humans have at least two qualitatively different systems of information storage, which are generally referred to as **declarative memory** and **nondeclarative memory** (Figure 30.1; see also Box A). Declarative memory is the storage (and retrieval) of material that is available to consciousness and can be expressed by language (hence, "declarative"). Examples of declarative memory are the ability to remember a telephone number, a song, or the images of some past event. Nondeclarative memory (sometimes referred to as *procedural memory*), on the other hand, is not available to consciousness, at least not in any detail. Such memories involve skills and associations that are, by and large, acquired and retrieved at an unconscious level. Remembering how to dial the telephone, how to sing a song, how to efficiently inspect a scene, or making the myriad associations that occur continuously are all examples of memories that fall in this category. It is difficult or impossible to say how we do these things, and we are not conscious of any particular memory during their occurrence. In fact, thinking about such activities may actually inhibit the ability to perform them efficiently (thinking about exactly how to stroke a tennis ball or swing a golf club often makes matters worse).

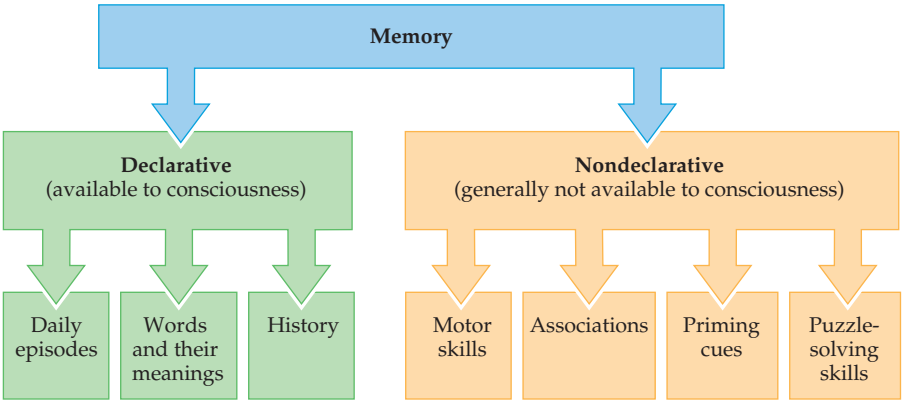


Figure 30.1 The major qualitative categories of human memory. Declarative memory includes those memories that can be brought to consciousness and expressed as remembered events, images, sounds, and so on. Nondeclarative, or procedural, memory includes motor skills, cognitive skills, simple classical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

While it makes good sense to divide human learning and memory into categories based upon the accessibility of stored information to conscious awareness, this distinction becomes problematic when considering learning and memory processes in animals. From an evolutionary point of view, it is unlikely that declarative memory arose *de novo* in humans with the development of language. Although some researchers continue to argue for different classifications in humans and other animals, recent studies suggest that similar memory processes operate in all mammals and that these memory functions are subserved by homologous neural circuitry. In other mammals, declarative memory typically refers to the storage of information which could, in principle, be declared through language (e.g., "the cheese is in the box in the corner") and that is dependent on the integrity of the medial temporal lobe and its associated structures (discussed later in the chapter). Nondeclarative memory in other animals, as in humans, can be thought of as referring to the learning and storage of sensory associations and motor skills that are not dependent on the medial temporal portions of the brain.

Temporal Categories of Memory

In addition to the types of memory defined by the nature of what is remembered, memory can also be categorized according to the *time* over which it is effective. Although the details are still 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 routine ability to hold ongoing experiences in mind for

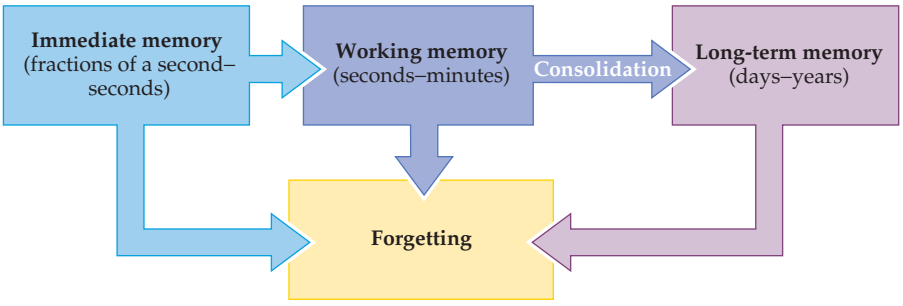


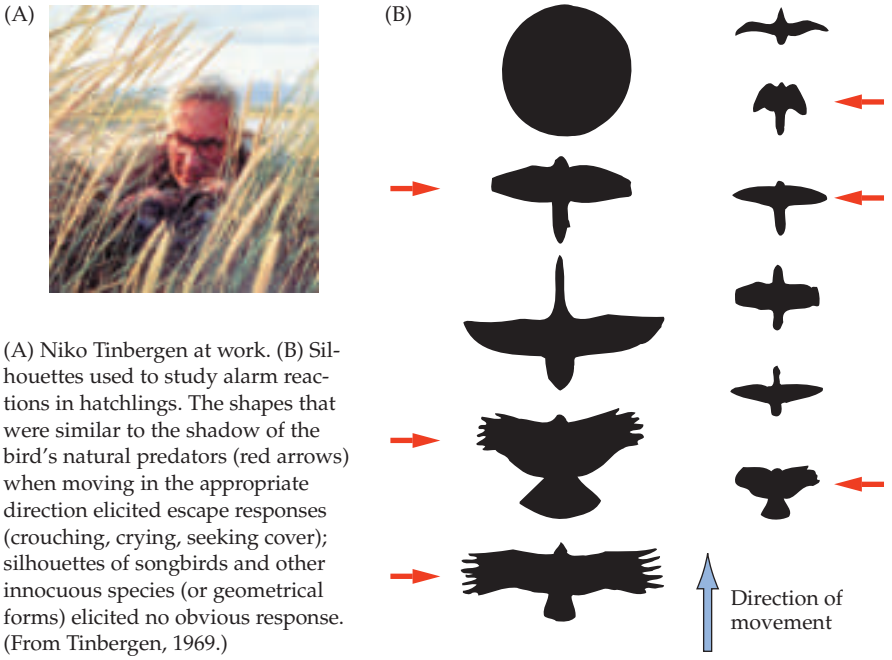
Figure 30.2 The major temporal categories of human memory.

Box A

Phylogenetic Memory

A category of information storage not usually considered in standard accounts is memories that arise from the experience of the 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 has typically encountered in its environment. 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, phylogenetic and ontogenetic memories are based on neuronal connectivity.)

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 in 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. Having 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.



(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 (crouching, crying, seeking cover); silhouettes of songbirds and other innocuous species (or geometrical forms) elicited no obvious response. (From Tinbergen, 1969.)

Despite the relatively scant attention paid to this aspect of memory, it is probably the most important component of the stored information in the brain that determines whether or not an individual survives long enough to reproduce.

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fractions of a second. The capacity of immediate memory is very large and each sensory modality (visual, verbal, tactile, and so on) appears to have its own memory register.

Working memory, the second temporal category, is the ability to hold information in mind for seconds to minutes once the present moment has

TABLE 30.1
The Fallibility of Human Memory[a]

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

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

passed. An everyday example of working memory is searching for a lost object; working memory allows the hunt to proceed efficiently, avoiding places already inspected. A conventional way of testing the integrity of working memory at the bedside is to present a string of randomly ordered digits, which the patient is then asked to repeat; surprisingly, the normal "digit span" is only 7–9 numbers.

The third temporal category is **long-term memory** and entails the retention of information in a more permanent form of storage for days, weeks, or even a lifetime. There is general agreement that the so-called **engram**—the physical embodiment of the long-term memory in neuronal machinery—depends on long-term changes in the efficacy of transmission of the relevant synaptic connections, and/or the actual growth and reordering of such connections. As discussed in Chapter 24, there is good reason to think that both these varieties of synaptic change occur.

Evidence for a continual transfer of information from working memory to long-term memory, or **consolidation** (Figure 30.2), is apparent in the phenomenon of **priming**. Priming 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., whether the words are verbs, adjectives, or nouns). Sometime thereafter (e.g., 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 whatever letters come to mind. The test list actually includes fragments of words that were presented in the first test, mixed among fragments of words that were not. Subjects fill in the letters to make the words that were presented earlier at a higher rate than expected by chance, even though they have no specific memory of the words that were seen initially; moreover, they are faster at filling in letters to make words that were seen earlier than new words. Priming shows that information previously presented is 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.

Despite the prevalence of such transfer, the information stored in this process is not particularly reliable. Consider, for instance, 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 bias 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.

The Importance of Association in Information Storage

The normal human capacity for remembering relatively meaningless information is surprisingly limited (as noted, a string of about 7–9 numbers or other arbitrary items). This capacity, however, can be increased dramatically. For example, a college student who for some months spent an hour each day practicing the task of remembering randomly presented numbers was able to recall a string of up to about 80 digits (Figure 30.3). He did this primarily

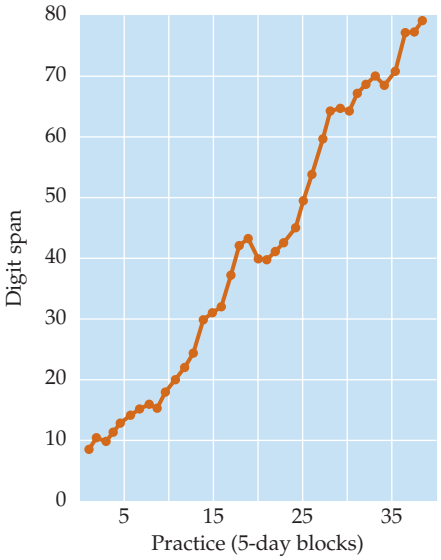

Figure 30.3 Increasing the digit span by practice (and the development of associational strategies). During many months involving one hour of practice a day for 3–5 days a week, this subject increased his digit span from 7 to 79 numbers. Random digits were read to him at the rate of one per second. If a sequence was recalled correctly, one digit was added to the next sequence. (After Ericsson et al., 1980.)

by making subsets of the string of numbers 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 *association* is used by most professional "mnemonists," who amaze audiences by apparently prodigious feats of memory. Similarly, a good chess player can remember the position of many more pieces on a briefly examined board than a poor player, presumably because the positions have much more significance for individuals who know the intricacies of the game than for neophytes (Figure 30.4). Thus, the capacity of working memory very much depends on

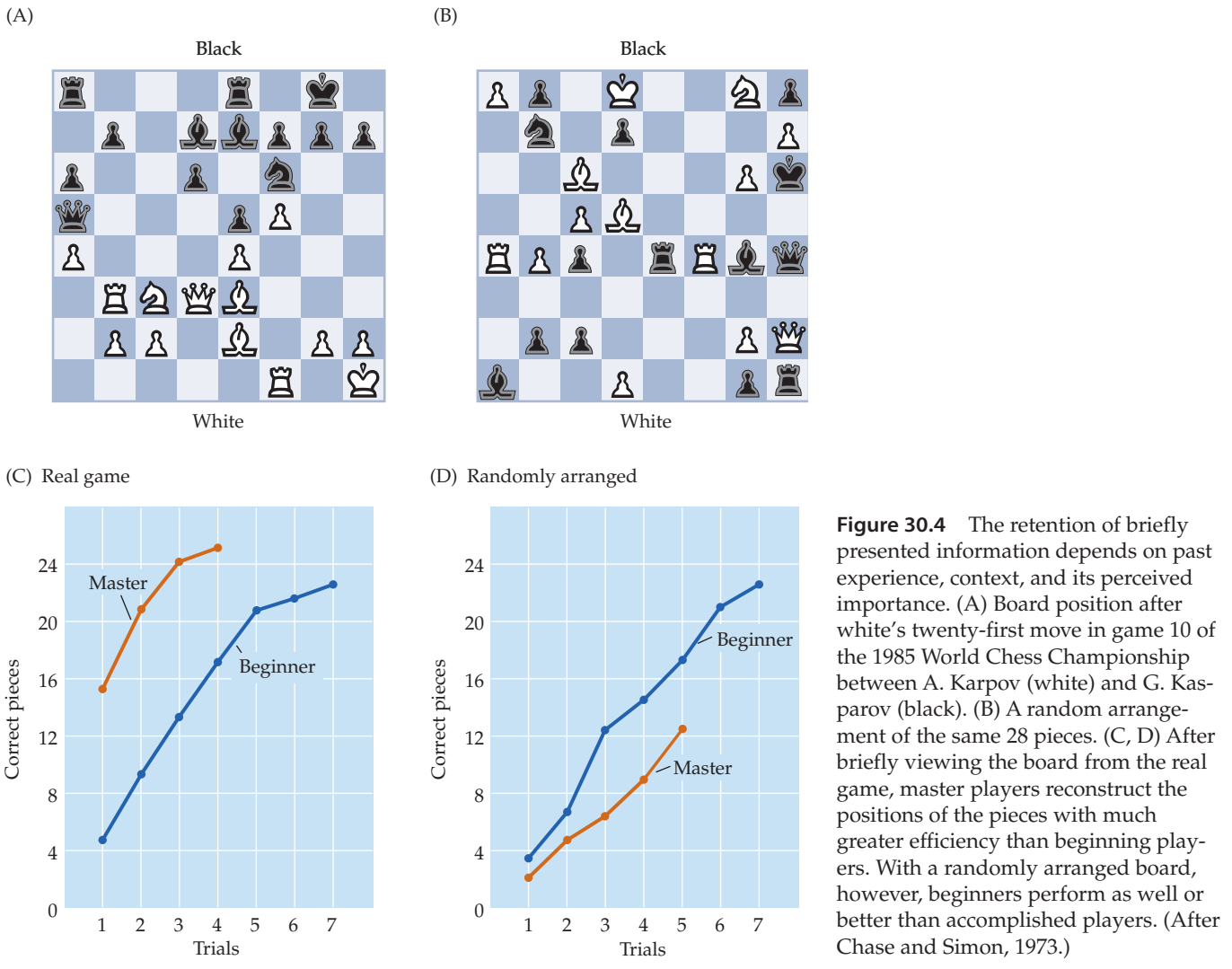

Figure 30.4 The retention of briefly presented information depends on past experience, context, and its perceived importance. (A) Board position after white's twenty-first move in game 10 of the 1985 World Chess Championship between A. Karpov (white) and G. Kasparov (black). (B) A random arrangement 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 or better than accomplished players. (After Chase and Simon, 1973.)

what the information in question means to the individual and how readily it can be associated with information that has already been stored.

The ability of humans to remember significant information in the normal course of events is, in fact, enormous. Consider Arturo Toscanini, the late conductor of the NBC Philharmonic Orchestra, who 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 because he had 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.

A parallel example of a prodigious quantitative memory is the mathematician Alexander Aitken. After an undistinguished career in elementary school, the 13-year-old Aitken was greatly taken with the manipulation of numbers. For the next four years he undertook, as a personal challenge, to master mental calculation. He began by memorizing the value of π to 1000 places, and could soon do calculations in his head with such facility that he became a local celebrity. When asked for the squares of three-digit numbers, he was able to give these almost instantly. The square roots for each were produced to five significant digits in 2–3 seconds; the squares of four-digit numbers allegedly took him about 5 seconds. Aitken went on to become a professor of mathematics at Edinburgh and was eventually elected a Fellow of the Royal Society for his contributions to numerical mathematics, statistics, and matrix algebra. At the age of 30 or so, he began to lose his enthusiasm for "mental yoga," as he called his penchant. In part, his waning enthusiasm stemmed from the realization that the advent of calculators was making his prowess obsolete (it was then 1930). He also discovered that the last 180 digits of π that he had memorized as a boy were wrong; he had taken the values from the published work of another mental calculator, who erred in an era when there was no way to check the correct value. In fact, Aitken's feat has long since been superseded. In 1981, an Indian mnemonist memorized the value of π to 31,811 places, only to have a Japanese mnemonist increase this record to 40,000 places a few years later!

Toscanini's and Aitken's mental processes in these feats were not rote learning, but a result of the fascination that aficionados bring to their special interests (Box B). Although few can boast the mnemonic prowess of such individuals, the human ability to remember the things that deeply interest us—whether baseball statistics, soap opera plots, or the details of brain structure—is amazing.

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 should get the higher marks. Common sense indicates that, were it not for forgetting, our brains would be impossibly burdened with the welter of useless information that is briefly encoded in our immediate memory "buffer." In fact, the human brain is very good at forgetting. In addition to the unreliable performance on tests such as the example in Table 30.1, Figure 30.5 shows that the memory of the appearance of a penny (an icon seen

Box B

Savant Syndrome

A fascinating developmental anomaly of human memory is seen in rare individuals who until recently were referred to as *idiots 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 to 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 severely retarded.

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 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 three, particularly those providing factual information and lists (e.g., telephone directories and dictionaries). At about six or seven 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 an ability in their areas of expertise that exceeds the competency of normally intelligent individuals who focus passionately on a particular subject (several examples are given in the text). 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.

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thousands of times since childhood) is uncertain at best, and that people gradually forget what they have seen over the years (TV shows, in this case). Clearly we forget things that have no particular importance, and unused memories deteriorate over time.

The ability to forget unimportant information may be as critical for normal life as retaining information that is significant. One sort of evidence for this presumption is rare individuals who have difficulty with the normal erasure of information. Perhaps the best-known case is a subject studied over several decades by the Russian psychologist A. R. Luria, who referred to the

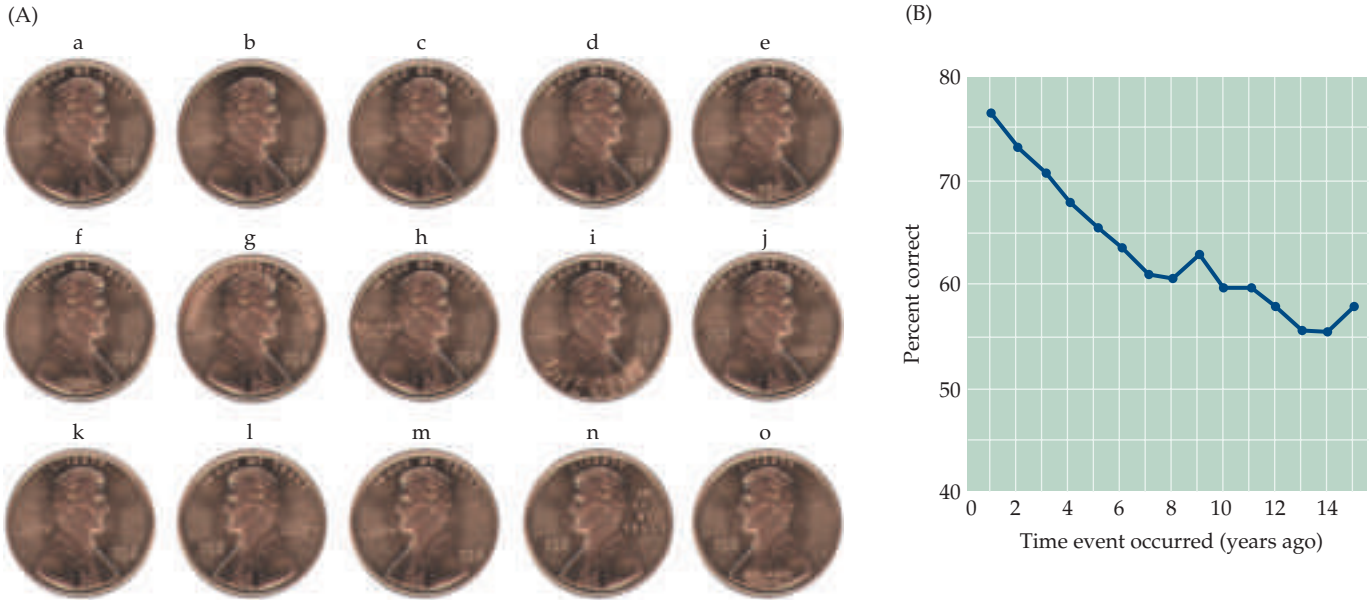


Figure 30.5 Forgetting. (A) Different versions of the "heads" side of a penny. Despite innumerable exposures to this familiar design, few people are able to pick out (a) as the authentic version. Clearly, repeated information is not necessarily retained. (B) The deterioration of long-term memories was 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.)

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, however, did not always serve him well. 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)

TABLE 30.2
Causes of Amnesia

Causes	*Examples*	*Site of damage*
Vascular occlusion of both posterior cerebral arteries	Patient R.B. (Box C)	Bilateral medial temporal lobe, the hippocampus in particular
Midline tumors	—	Medial thalamus bilaterally (hippocampus and other related structures if tumor is large enough)
Trauma	Patient N.A. (Box C)	Bilateral medial temporal lobe
Surgery	Patient H.M. (Box C)	Bilateral medial temporal lobe
Infections	Herpes simplex encephalitis	Bilateral medial temporal lobe
Vitamin B_1 deficiency	Korsakoff's syndrome	Medial thalamus and mammillary bodies
Electroconvulsive therapy (ECT) for depression	—	Uncertain

> 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

Although forgetting is a normal and apparently essential mental process, it can also be pathological, a condition called **amnesia**. Some of the causes of memory loss are listed in Table 30.2. 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 stored, as discussed in the next section.

Brain Systems Underlying Declarative Memory Formation

Three extraordinary clinical cases of amnesia have been especially revealing about the brain systems responsible for the short-term storage and consolidation of declarative information and are now familiar to neurologists and psychologists as patients H.M., N.A., and R.B. (Box C). Taken together, these cases provide dramatic evidence of the importance of midline diencephalic and medial temporal lobe structures—the **hippocampus**, in particular—in establishing new declarative memories (Figure 30.6). These patients also demonstrate that there is a different anatomical substrate for anterograde and retrograde amnesia, since in each of these individuals, memory for events *prior* to the precipitating injury was largely retained.

The devastating deficiency is (or was, in the case of R.B.) the inability to establish new memories. Retrograde amnesia—the loss of memory for events preceding an injury or illness—is more typical of the generalized

Box C

Clinical Cases That Reveal the Anatomical Substrate for Declarative Memories

The Case of H.M.

H.M. had suffered minor seizures since age 10 and major seizures since age 16. 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. 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 his life was changed radically.

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 (that is, his ability to form procedural 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 indicate a profound loss of short-term declarative memory function.

During the subsequent decades, H.M. has been studied extensively, primarily by Brenda Milner and her colleagues at the Montreal Neurological Institute. His memory deficiency has continued unabated, and, according to Milner, he has little idea who she is in spite of their acquaintance for nearly 50 years. Sadly, he has gradually come to appreciate his predicament. "Every day is alone," H.M. reports, "whatever enjoyment I've had and whatever sorrow I've had."

The Case of 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.

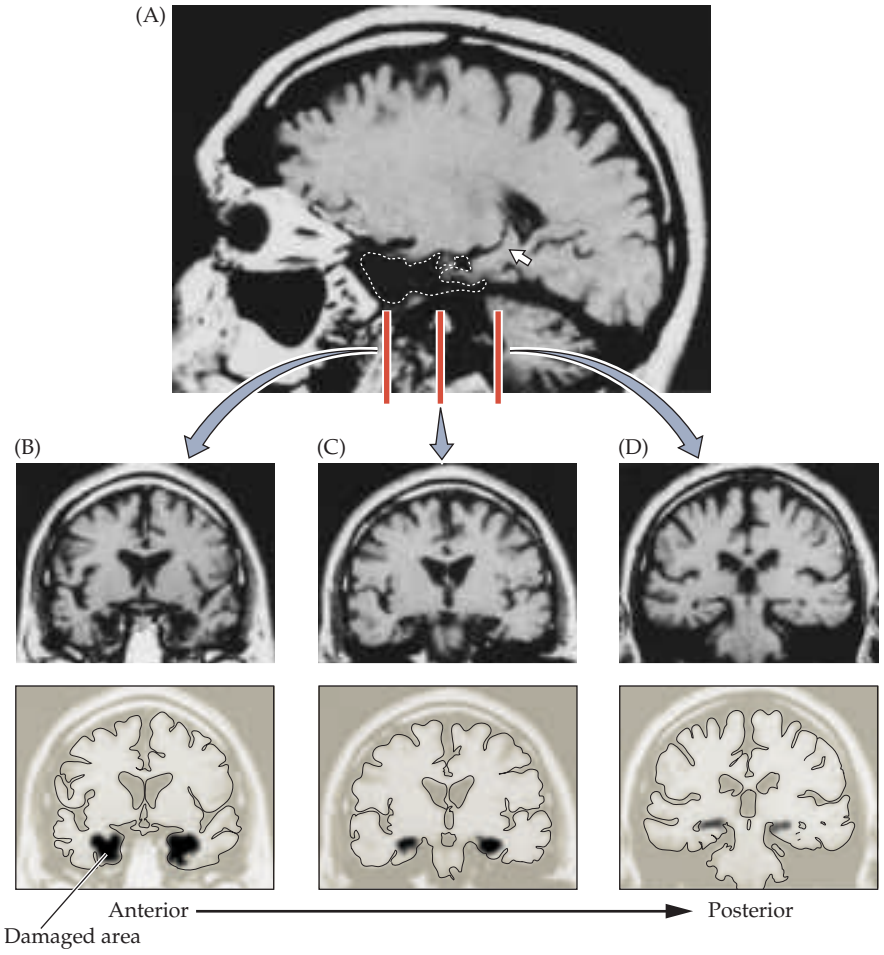
N.A. was assembling a model airplane in his barracks room while, unbeknownst to him, his roommate was practicing thrusts and parries with a miniature fencing foil behind N.A.'s chair. N.A. turned suddenly and was stabbed through the right nostril. The foil penetrated the cribriform plate (the structure 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 a right-sided 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 the medial temporal lobe, mostly on the right side; the mammillary bodies also appeared to be missing bilaterally. 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 over 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 procedural 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. Watching television is difficult because he tends to forget the storyline during commercials. On the other hand, his memory for events prior to 1960 is extremely good; indeed, his lifestyle tends to reflect the 1950s.

The Case of 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., his IQ was normal (111), and he showed no evidence of cognitive defects other than memory impairment. R.B. was tested extensively for the next five 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 ability to establish new declarative memories. When R.B. died in 1983 of congestive heart failure, 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.



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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 have been ablated (black shading). (From Corkin et al., 1997.)

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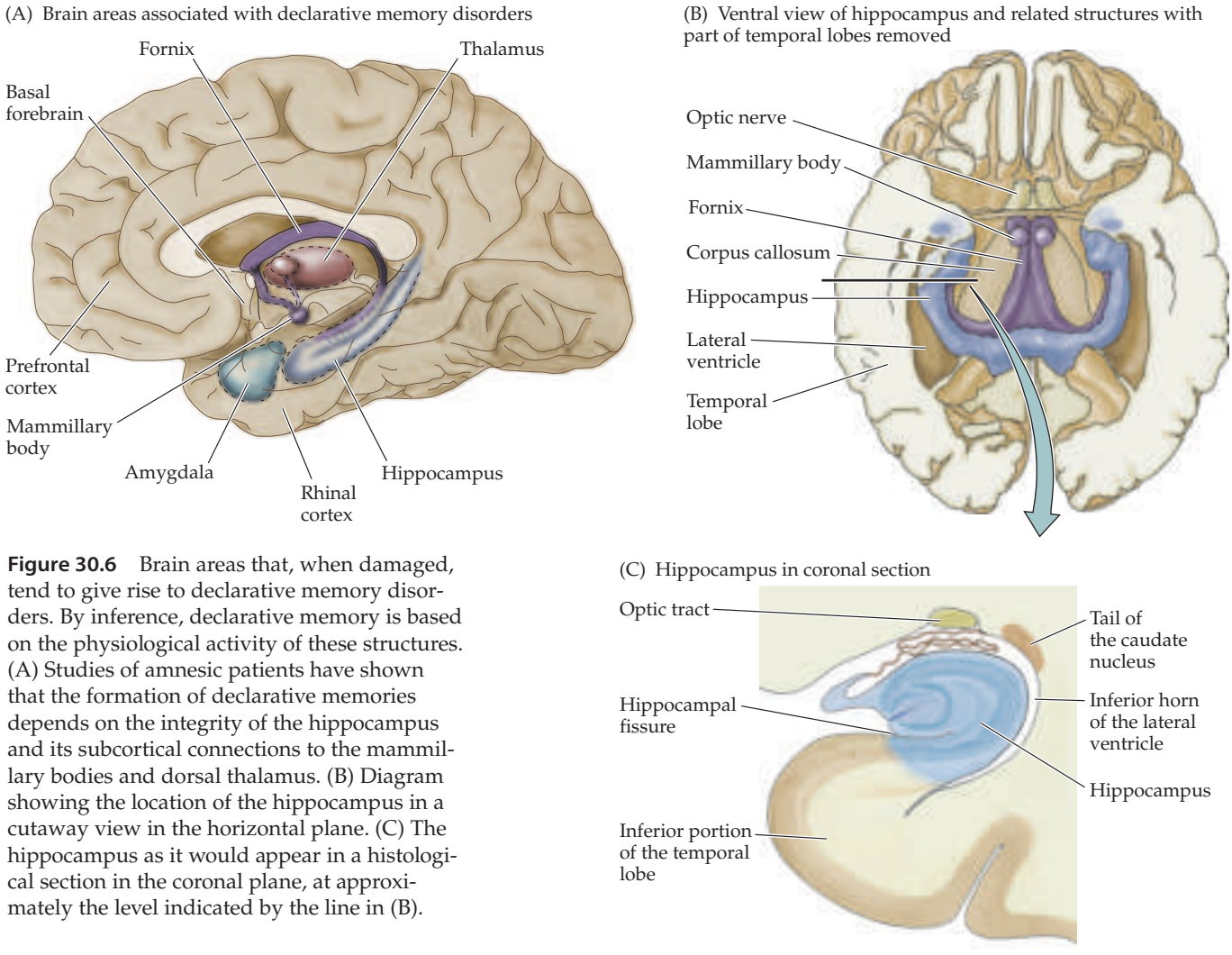


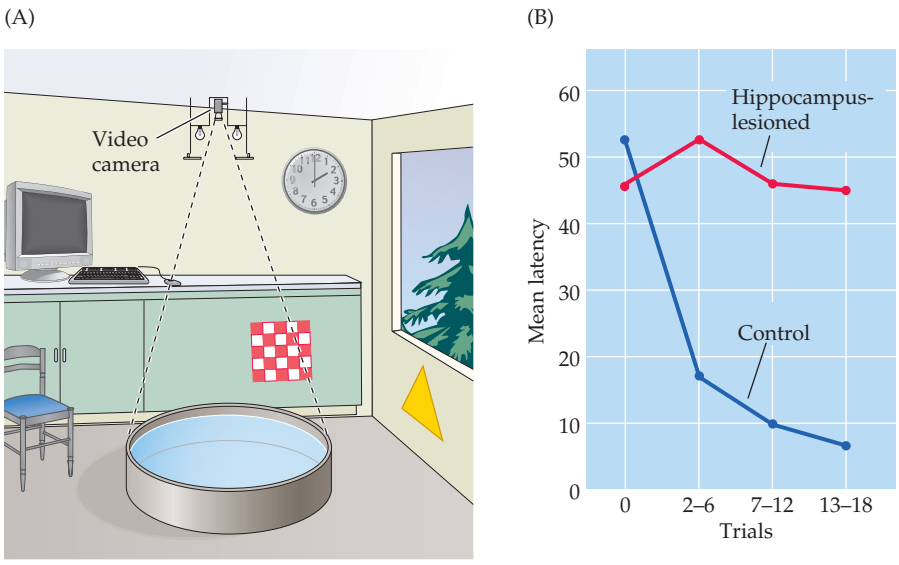
Figure 30.6 Brain areas that, when damaged, tend to give rise to declarative memory disorders. By inference, declarative memory is based on the physiological activity of these structures. (A) Studies of amnesic patients have shown that the formation of declarative memories depends on the integrity of the hippocampus and its subcortical connections to the mammillary bodies and dorsal thalamus. (B) Diagram showing the location of the hippocampus 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).

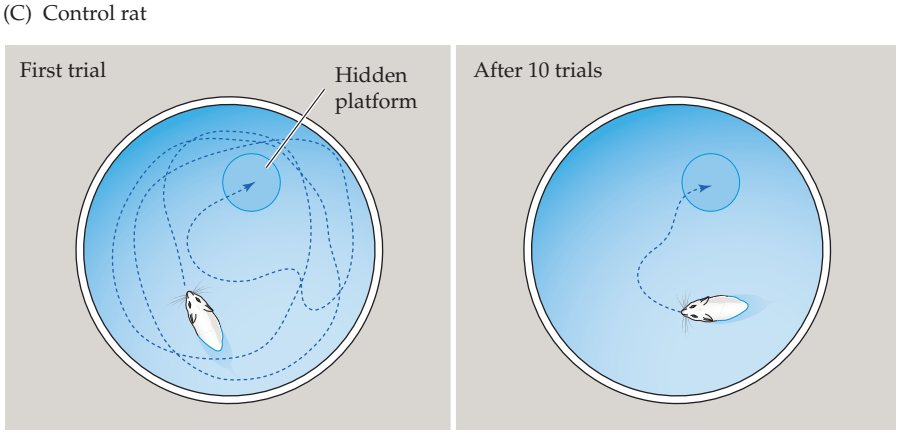
lesions associated with head trauma and neurodegenerative disorders, such as Alzheimer's disease (Box D). Although a degree of retrograde amnesia can occur with the more focal lesions that cause anterograde amnesia, the long-term storage of memories is presumably distributed throughout the brain (see the next section). Thus, the hippocampus and related diencephalic structures indicated in Figure 30.6 form and consolidate declarative memories that are ultimately stored elsewhere.

Other causes of amnesia have also provided some insight into the parts of the brain relevant to various aspects of memory (see Table 30.2). **Korsakoff's syndrome**, for example, occurs in chronic alcoholics as a result of thiamine (vitamin B_1) deficiency. In such cases, loss of brain tissue occurs bilaterally in the mammillary bodies and the medial thalamus, for reasons that are not well understood.

Studies of animals with lesions of the medial temporal lobe have largely corroborated these findings with 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; note that the pool is surrounded by prominent visual landmarks (Figure 30.7). 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. Rats with lesions to the hippocampus and nearby structures cannot learn to find the platform, suggesting that remembering the location of the platform





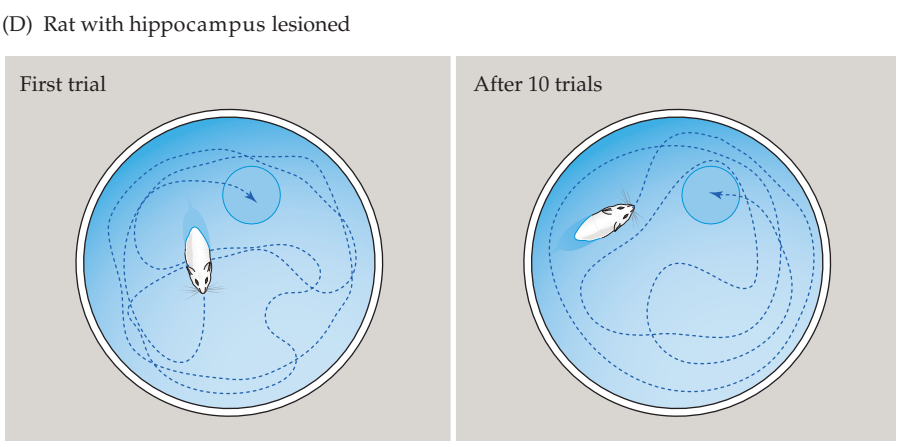


Figure 30.7 Spatial learning and memory in rodents depends on the hippocampus. (A) Rats are placed in a circular tank about the size and shape of a child's wading pool filled with opaque (milky) water. The surrounding environment contains visual cues such as windows, doors, a clock, and so on. A small 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) 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 rats (C) and hippocampal lesioned rats (D) 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).

relative to the configuration of 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 (see Figure 25.13). These studies suggest that primates and other mammals depend on medial temporal structures such as the hippocampus and parahippocampal gyrus to encode and consolidate memories of events and objects in time and space, just as humans use these same brain regions for the initial encoding and consolidation of declarative memories.

Brain Systems Underlying Long-Term Storage of Declarative Memory

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 quite clearly that such information is *not* stored in the midline diencephalic and medial temporal lobe structures that are affected in anterograde amnesia). Nonetheless, a good deal of evidence implies that the cerebral cortex is the major long-term repository for many aspects of declarative memory.

One line of evidence comes from observations of patients undergoing electroconvulsive therapy (ECT). Individuals with severe depression are often treated by the passage of enough electrical current through the brain to cause the equivalent of a full-blown seizure (this procedure is done under anesthesia, in well-controlled circumstances). This remarkably useful treatment was discovered because depression in epileptics was perceived to remit after a spontaneous seizure (see Box C in Chapter 24). 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 even their recall of events of the previous 1–3 years can be affected. Animal studies (rats tested for maze learning, for example) have confirmed the amnesic consequences of ECT. The memory loss usually clears over a period of weeks to months. However, to mitigate this side effect (which may be the result of excitotoxicity; see Box B in Chapter 6), ECT is often delivered to only one hemisphere at a time. The nature of amnesia following ECT supports the conclusion that long-term declarative memories are widely stored in the cerebral cortex, since this is the part of the brain predominantly affected by this therapy.

A second line of evidence comes from patients with damage to association cortex outside the medial temporal lobe. Since different cortical regions have different cognitive functions (see Chapters 25 and 26), it is not surprising that these sites store information that reflects the cognitive function of that part of the brain. For example, the lexicon 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 26). Presumably, the widespread connections of the hippocampus to the language areas serve to consolidate declarative information in these and other language-related cortical sites (Figure 30.8). By the same token, the inability of patients with temporal lobe lesions to recognize objects and/or faces suggests that such memories are stored there (see Chapter 25).

A third sort of evidence supporting the hypothesis that declarative memories are stored in cortical areas specialized for processing particular types of

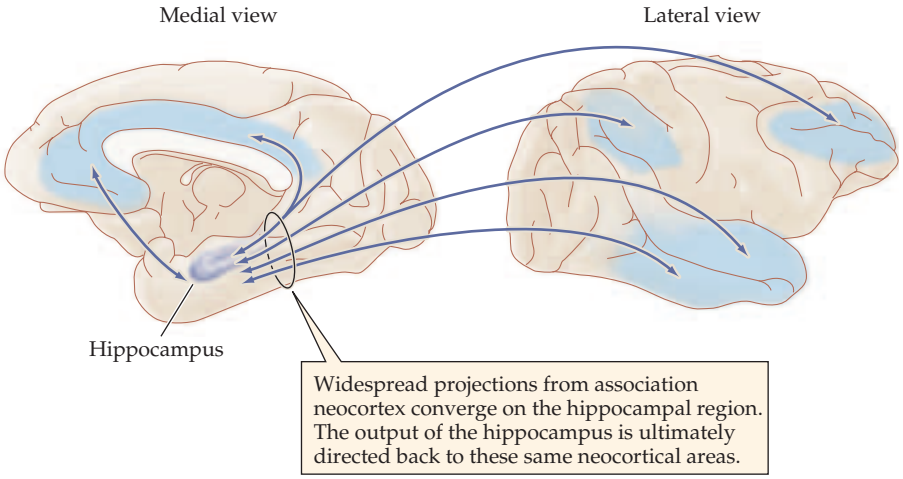


Figure 30.8 Connections between the hippocampus and possible declarative memory storage sites. The rhesus monkey brain is shown because these connections are much better documented in non-human primates than in humans. Projections from numerous cortical areas converge on the hippocampus and the related 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.)

information comes from neuroimaging of human subjects recalling vivid memories. In one such study, subjects first examined 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—such as faces, houses, or chairs—tend to reactivate the same small regions of the visual association cortex that were activated when the objects were actually perceived (Figure 30.9).

These neuroimaging studies reinforce the conclusion that declarative memories are stored widely in specialized areas of the cerebral cortex. Retrieving such memories appears to involve the medial temporal lobe, as well as regions of the frontal cortex. Frontal cortical areas located on the dorsolateral and anterolateral aspect of the brain, in particular, are activated when normal subjects attempt to retrieve declarative information from long-term memory. Moreover, patients with damage to these areas often fail to accurately recall the details of a memory and sometimes resort to confabulation to fill in the missing information. Finally, whereas the ability of patients such as H.M., N.A., and R.B. to remember facts and events from the period of their lives preceding their lesions clearly demonstrates that the medial temporal lobe is not necessary for retrieving declarative information held in long-term memory, other studies have suggested that these structures may be important for recalling declarative memories during the early stages of consolidation and storage in the cerebral cortex.

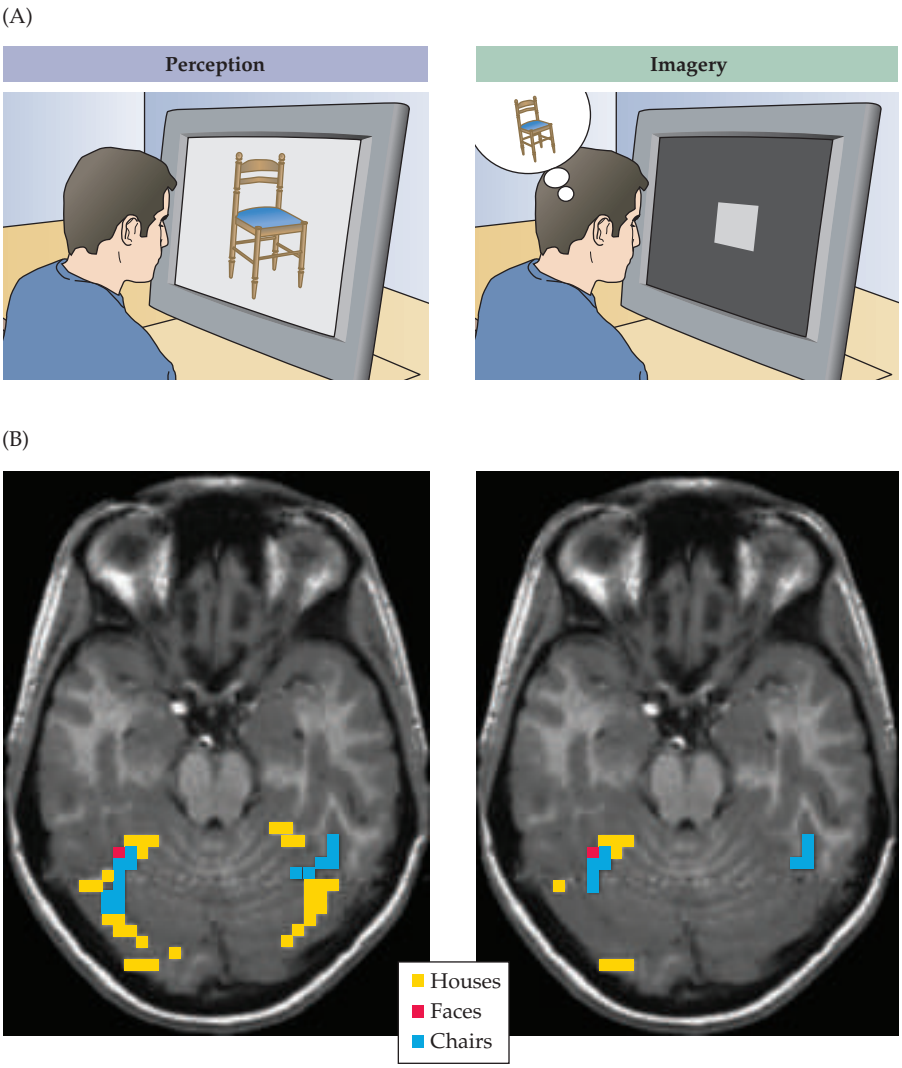


Figure 30.9 Reactivation of visual cortex during vivid remembering of visual view images. (A) Subjects were instructed to view either images of objects (houses, faces, and chairs) (left) or imagine the objects in the absence of the stimulus (right). (B) (Left) Bilateral regions of ventral temporal cortex are specifically activated during perception of houses (yellow), faces (red), and chairs (blue). (Right) When subjects recall these objects, the same regions preferentially activated during the perception of each object class are reactivated. (After Ishai et al., 2000).

Brain Systems Underlying Nondeclarative Learning and Memory

H.M., N.A., and R.B. had no difficulty establishing or recalling nondeclarative memories, indicating that this information is laid down by using an anatomical substrate different from that used in declarative memory formation. Nondeclarative memory apparently involves the basal ganglia, prefrontal cortex, amygdala, sensory association cortex, and cerebellum, but not the medial temporal lobe or midline diencephalon. In support of this interpretation, perceptual priming (the influence of previously studied information on subsequent performance, unavailable to conscious recall) 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 sensory-motor 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 cause profound deficits in classical eyeblink conditioning without interfering with the

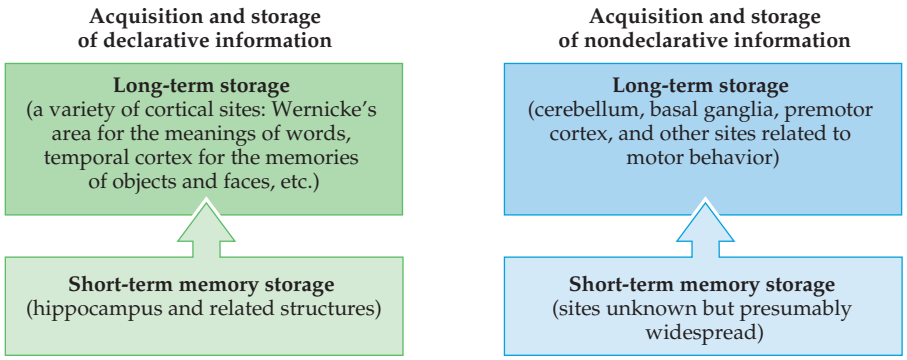


Figure 30.10 Summary diagram of the acquisition and storage of declarative versus nondeclarative information.

ability to lay down new declarative memories. Evidence from such double-dissociations endorses the idea that independent brain systems govern the formation and storage of declarative and nondeclarative memories.

A brain system that appears to be especially important for complex motor learning involves the signaling loops that connect the basal ganglia and prefrontal cortex (see Chapter 17). Damage to either structure profoundly interferes with the ability to learn new motor skills. Thus, patients with Huntington's disease, which causes atrophy of the caudate and putamen (see Figure 17.9B), 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 (see Figure 17.9A), patients with Parkinson's disease show similar deficits in motor skill learning, 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 30.10. The generality of the diagram only 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 instantiated in an extensive network of neurons whose activity depends on synaptic weightings that have been molded and modified by experience.

Memory and Aging

Although it is all too obvious that our outward appearance changes with age, we tend to imagine that the brain is much more resistant to the ravages of time. Unfortunately, the evidence suggests that this optimistic view is not justified. From early adulthood onward, the average weight of the normal human brain, as determined at autopsy, steadily decreases (Figure 30.11). 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 (i.e., neuropil) that are lost as

Box D

Alzheimer's Disease

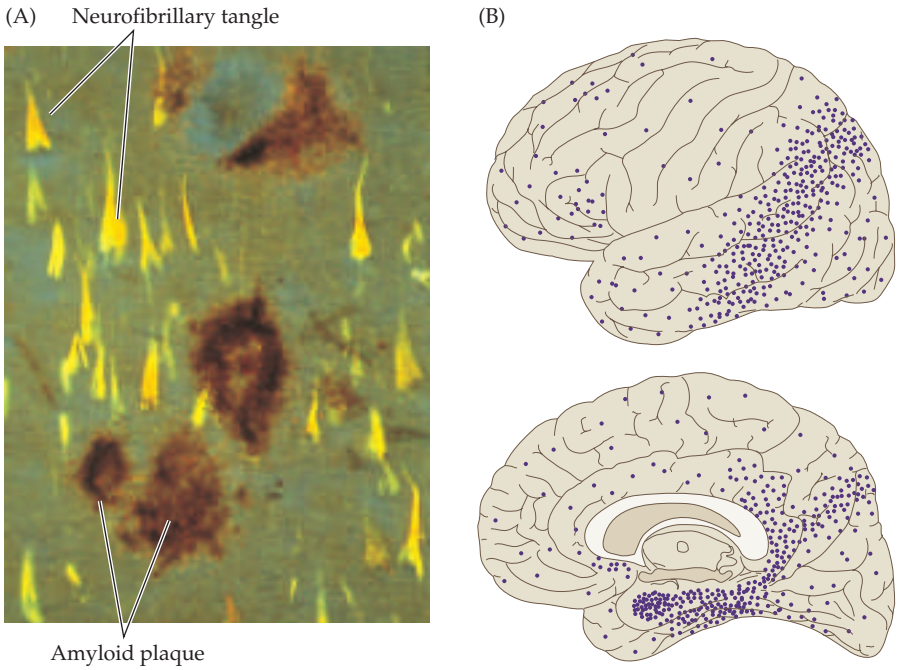
Dementia is a syndrome characterized by failure of recent memory and other intellectual functions that is usually insidious in onset but steadily progresses. Alzheimer's disease (AD) is the most common dementia, accounting for 60–80% of cases in the elderly. It afflicts 5–10% of the population over the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

The tentative diagnosis of Alzheimer's disease is based on these characteristic clinical features, and can only be confirmed by the distinctive cellular pathology evident on postmortem examination of the brain. The histopathology consists of three principal features (illustrated in the figure): (1) collections of intraneuronal cytoskeletal filaments called *neurofibrillary tangles*; (2) extracellular deposits of an abnormal protein in a matrix 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 selected brainstem nuclei (especially the basal forebrain nuclei).

Although the vast majority of AD cases arise sporadically, the disorder is inherited in an autosomal dominant pattern in a small fraction (less than 1%) of patients. Identification of the mutant gene in a few families with an early-onset autosomal dominant form of the disease has provided considerable insight into the kinds of processes that go awry in Alzheimer's.

Investigators suspected that the mutant gene responsible for familial AD might reside on chromosome 21, primarily because similar clinical and neuropathologic features often occur in individuals with Down's syndrome (a syndrome typically caused by an extra copy of chromosome 21), but with a much earlier onset (at about age 30 in most cases). The prominence of amyloid deposits in AD further suggested that a mutation of a gene encoding amyloid precursor protein is somehow involved. The gene for amyloid precursor protein (APP) was cloned by D. Goldgaber and 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 (*presenilin 1* and *presenilin 2*). Thus, mutation of any one of several genes appears to be sufficient to cause a heritable form of AD.

The most common form of Alzheimer's occurs late in life, and although the relatives of affected individuals are at a greater risk, the disease is clearly not inherited in any simple sense. The central role of APP in the families with



(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 from Roses, 1995, courtesy of Gary W. Van Hoesen; B after Blumenfeld, 2002, based on Brun and Englund, 1981.)

the early-onset form of the disease nonetheless suggested that APP might be linked to the chain of events culminating in the "spontaneous" forms of Alzheimer's disease. In particular, biochemists Warren Strittmatter and Guy Salvesen theorized that pathologic deposition of proteins complexed with a derivative of APP might be responsible. To test this idea, they immobilized a recombinant form of the APP derivative on nitrocellulose paper and searched for proteins in the cerebrospinal fluid of patients with Alzheimer's disease 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 a discovery made by Margaret Pericak-Vance, Allen Roses, and their colleagues at Duke University Medical Center, who found that affected members of some families with the late-onset form of the inherited disease exhibited an association with genetic markers on chromosome 19. This finding was of particular interest because a gene encoding an isoform of apolipoprotein E (the *ε4* allele) is located in the same region of chromosome 19 implicated by the family studies. As a result, they began to explore the association of the different alleles of apolipoprotein E with affected members in families with a late-onset but inherited form of Alzheimer's disease.

There are three major alleles of apolipoprotein E, *ε2*, *ε3*, and *ε4*. The frequency of allele *ε3* in the general population is 0.78, and the frequency of allele *ε4* is 0.14. The frequency of the ε*4* allele in late-onset familial AD patients, however, is 0.52—almost 4 times higher than the general population. Thus, the inheritance of the *ε4* allele is a risk factor for late-onset AD. In fact, people homozygous for *ε4* are about 8 times more likely to develop AD compared to individuals homozygous for ε*3*. Among individuals in late-onset Alzheimer's families with no copies of *ε4*, only 20% develop AD by age 75 compared to 90% of individuals with two copies of *ε4*. An increased association of the *ε4* allele has also been shown in the sporadic form of AD, an especially important discovery because this category constitutes by far the most common form of the disease.

It is not known whether the ε*4* allele of ApoE itself is responsible for the increased risk, or whether it is linked to another gene on chromosome 19 that is the real culprit. The fact that ApoE binds avidly to amyloid plaques in AD brains favors the idea that the *ε4* allele of ApoE itself is the problem. However, in contrast to the mutations of *APP* or *presenilin 1* and *presenilin 2* that cause familial forms of AD, inheriting the *ε4* form of ApoE is *not* sufficient to cause AD; rather, inheriting this gene simply increases the risk of developing AD. Moreover, some of the individuals with early-onset forms of familial AD do not have the *ε4* allele. Thus, a variety of related molecular anomalies appear to underlie AD.

A possible common denominator of AD at the cellular level is the "amyloid cascade" hypothesis. A prominent constituent of the amyloid plaques is an abnormal cleavage product of APP called amyloid-β peptide (or β-A4). The cascade hypothesis proposes that accumulation of β-A4 is critical to the pathogenesis of AD. Others, however, argue that extracellular deposition of β-A4 may not be a key event in the pathogenesis of AD because the density of the β-A4 plaques correlates only poorly with severity of the dementia (the degree of dementia being much better correlated with the density of neurofibrillary tangles). Moreover, a transgenic mouse model of AD based on a *presenilin 1* mutation exhibits neurodegeneration without amyloid plaque formation.

Clearly, AD has a complex pathology and probably reflects a variety of related molecular and cellular abnormalities. It is unlikely that this important problem will be understood without a great deal more research, much hyperbole in the lay press notwithstanding.

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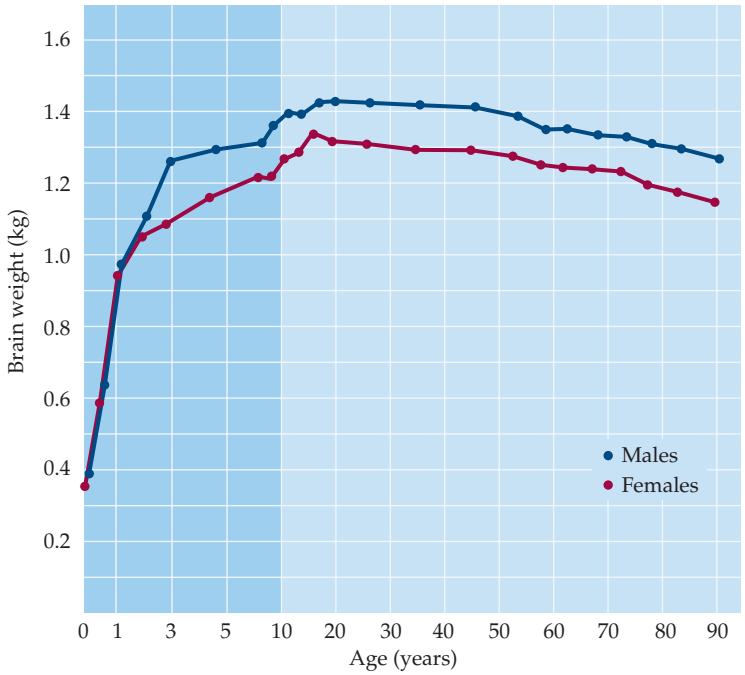

Figure 30.11 Brain size as a function of age. The human brain reaches its maximum size (measured by weight in this case) in early adult life and decreases progressively thereafter. This decrease evidently represents the gradual loss of neural circuitry in the aging brain, which presumably underlies the progressively diminished memory function in older individuals. (After Dekaban and Sadowsky, 1978.)

humans grow old (consistent with the idea that the networks of connections that represent memories—i.e., the engrams—gradually deteriorate).

These several 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 there is a large gray zone between individuals undergoing normal aging and patients suffering from age-related dementias such as Alzheimer's disease (see Box D).

Just as regular exercise slows the deterioration of the neuromuscular system with age, age-related neurodegeneration and associated cognitive decline may be slowed in elderly individuals who make a special effort to continue using the full range of human memory abilities (i.e, both declarative and nondeclarative memory tasks). 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 through compensatory activation of cortical tissue that is less fully used during remembering in poorly performing older adults (Figure 30.12).

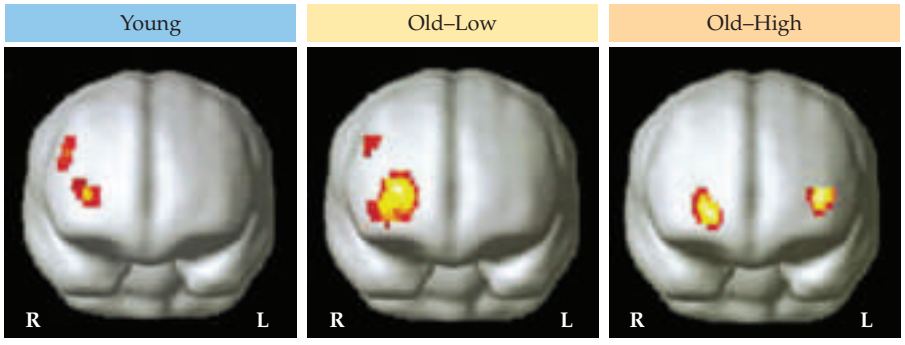

Figure 30.12 Compensatory activation of memory areas in high-functioning older adults. During remembering, activity in prefrontal cortex was restricted to the right prefrontal cortex (following radiological conventions, the brain images are left-right reversed) in both young participants and elderly 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).

Summary

Human memory entails a number of 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), and a separate system that concerns skills and associations that are essentially prelinguistic, operating at a largely 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 laying down new declarative memories, although not in storing them (a process that occurs primarily in the association cortices). In contrast, nondeclarative memories for motor and other unconscious skills depends on the integrity of the premotor cortex, basal ganglia, and cerebellum, and is not affected by lesions that impair the declarative memory system. The common denominator of these categories 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.

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