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CHAPTER

23

INTRODUCTION

It is difficult to study the brain without developing a sense of awe about how well it works. The sensory, motor, limbic, and modulatory systems contain billions of individual neural elements with enormous numbers of interconnections. As we saw in Chapter 22, the development of these connections is an orderly process that follows certain rules. Wiring the brain isn't magic—at least not entirely. But as impressive and orderly as prenatal development is, we are by no means complete creatures when we are born. From the moment we take our first breath, and possibly before, sensory stimuli modify our brain and influence our behavior. Indeed, one of the main goals of the first 20 years of life is to learn the skills we need to survive in the world. We learn an enormous number of things, some straightforward (snow is cold), and others more abstract (an isosceles triangle has two sides of equal length).

There is a close relationship between what we called experience-dependent brain development in Chapter 22 and what we call learning in this chapter. Visual experience during infancy is essential for the normal development of the visual cortex, but it also allows us to recognize an image of our mother's face. Visual development and learning probably use similar mechanisms, but at different times and in different cortical areas. Viewed in this way, learning and memory are the lifelong adaptations of brain circuitry to the environment. They enable us to respond appropriately to situations we have experienced before. This example also illustrates that a particular form of information is likely to be stored in the parts of the brain that normally process that type of information. Thus, we can expect different parts of the brain to participate in different types of memory.

In this chapter, we discuss the anatomy of memory, i.e., the different parts of the brain involved in storing particular types of information. In Chapter 24, we will focus on the elementary synaptic mechanisms that can store information in the brain.

TYPES OF MEMORY AND AMNESIA

Learning is the acquisition of new information or knowledge. **Memory** is the retention of learned information. We learn and remember many things, and it is important to appreciate that these various things may not be processed and stored by the same neural hardware. No single brain structure or cellular mechanism accounts for all learning. Moreover, the way in which information of a particular type is stored may change over time.

Declarative and Nondeclarative Memory

Psychologists have studied learning and memory extensively, and they have distinguished what appear to be different types. A useful distinction for our purposes is between declarative memory and nondeclarative memory.

During the course of our lives, we learn many facts—the capital of Thailand is Bangkok; the coyote will never catch the roadrunner. We also store memories of life's events—"I had Cheerios for breakfast"; "I heard a boring chemistry lecture yesterday." Memory for facts and events is called **declarative memory** (Figure 23.1). Declarative memory is what we usually mean by the word "memory" in everyday usage, but we actually remember many other things. These **nondeclarative memories** fall into several categories. The type we are most concerned with here is **procedural memory**, or memory for skills, habits, and behaviors. We learn to play the piano, throw a Frisbee, or tie our shoes, and somewhere that information is stored in our brain. In Chapter 18, we discussed learned fear, another type of nondeclara-

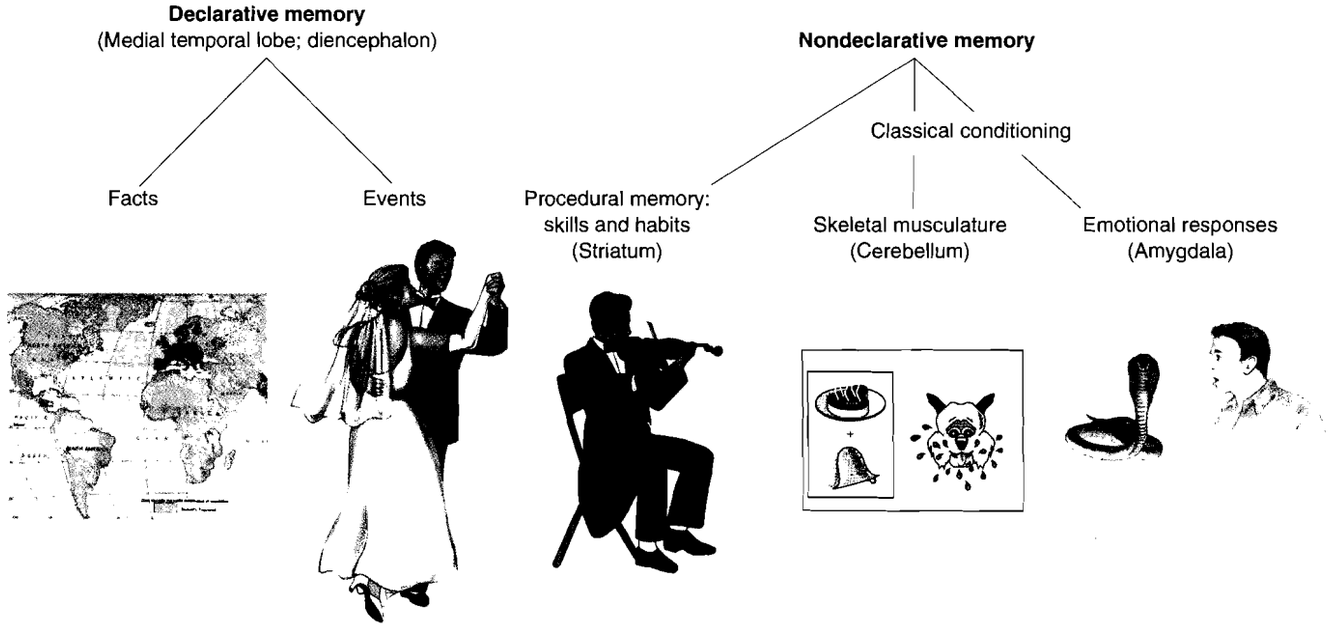

Figure 23.1
Types of declarative and nondeclarative memory. Brain structures thought to be involved in each type of memory are indicated. (This does not represent all types of memory.)

tive memory that involves the amygdala. Other forms of nondeclarative memory will be discussed in Chapter 24.

Generally, declarative memories are available for conscious recollection, and nondeclarative memories are not. The tasks we learn and the reflexes and emotional associations we have formed operate smoothly, however, without conscious recollection. As the old saying goes, you never forget how to ride a bicycle. You may not explicitly remember the day you first rode a two-wheeler on your own (the declarative part of the memory), but your brain remembers what to do when you're on one (the procedural part of the memory). Nondeclarative memory is also frequently called *implicit memory*, because it results from direct experience, and declarative memory is often called *explicit memory*, because it results from more conscious effort.

Another distinction is that declarative memories are often easy to form and are easily forgotten. By contrast, forming nondeclarative memories tends to require repetition and practice over a longer period, but these memories are less likely to be forgotten. Think of the difference between memorizing the capitals of foreign countries and learning to ski. While there is no clear limit to the number of declarative memories the brain can store, there can be great diversity in the ease and speed with which new information is acquired. Studies of humans with abnormally good memories suggest that the limit on the storage of declarative information is remarkably high (Box 23.1).

Long-Term and Short-Term Memory

Long-term memories are those that you can recall days, months, or years after they were stored. But not all memories make it into long-term storage. What did you have for dinner last night? You probably have no problem remembering. But how about dinner a week ago? Chances are that this memory has faded completely. Thus, it is useful to distinguish short-term memory (last night's dinner) from long-term memory. **Short-term memories** last on the order of seconds to hours and are vulnerable to disruption. For exam-

Box 23.1

OF SPECIAL INTEREST

An Extraordinary Memory

In the 1920s, a man named Sherashevsky came to see the Russian psychologist Aleksandr Luria. Thus began a 30-year study of the uncommon memory of this man Luria simply called S. Luria's fascinating description of this study is contained in the book *The Mind of a Mnemonist*. Luria initially studied S. by giving him conventional tests, such as memorizing lists of words, numbers, or nonsense syllables. He'd read the list once and then ask S. to repeat it. Much to Luria's surprise, he couldn't come up with a test S. could not pass. Even when 70 words were read in a row, S. could repeat them forward, backward, and in any other order. During the many years they worked together, Luria never found a limit to S.'s memory. In tests of his retention, S. demonstrated that he remembered lists he had previously seen even 15 years earlier!

How did he do it? S. described several factors that may have contributed to his great memory. One was his unusual sensory response to stimuli—he retained vivid images of things he saw. When shown a table of 50 numbers, he claimed it was easy to later read off numbers in one row or along the diagonal because he simply had to call up a visual image of the entire table. Interestingly, when he occasionally made errors in recalling tables of numbers written on a chalkboard, they appeared to be "reading" errors rather than memory errors. For instance, if the handwriting was sloppy, he would mistake a 3 for an 8 or a 4 for a 9. It was as if he was seeing the chalkboard and numbers all over again when he was recalling the information.

Another interesting aspect of S.'s sensory response to stimuli was a powerful form of *synesthesia*, a phenomenon in which sensory stimuli evoke sensations usually associated with different stimuli. For example, when S. heard a sound, in addition to hearing, he would see splashes of colored light and perhaps have a certain taste in his mouth.

After learning that his memory was unusual, S. left his job as a reporter and became a professional stage performer—a mnemonist. To remember huge lists of numbers or tables of words given by members of the audience trying to stump him, he complemented his lasting sensory responses to stimuli and his synesthesia with memory "tricks." To remember a long list of items, he made use of the fact that each item evoked some sort of visual image. As the list was read or written, S. imagined himself walking through his home town; as each item was given, he placed its evoked image along his walk—the image evoked by item 1 by the mailbox, the image for item 2 by a bush, and so on. To recall the items, he walked the same route and picked up the items he had put down. Though we may not have the complex synesthetic sensations of S., this ancient technique of making associations with familiar objects is one we all can use.

Not everything about S.'s memory was to his advantage. While the complex sensations evoked by stimuli helped him remember lists of numbers and words, they interfered with his ability to integrate and remember more complex things. He had trouble recognizing faces because each time a person's expression changed, he would also "see" changing patterns of light and shade, which would confuse him. He also wasn't very good at following a story read to him. Rather than ignoring the exact words and focusing on the important ideas, S. was overwhelmed by an explosion of sensory responses. Imagine how bewildering it would be to be bombarded by constant visual images evoked by each word, plus sounds and images evoked by the tone of voice of the person reading the story. No wonder S. had trouble!

S. also experienced the inability to forget. This became a particular problem when he was performing as a professional mnemonist and was asked to remember things written on a chalkboard. He would see things that had been written there on many occasions. Although he tried various tricks to forget old information, such as mentally erasing the board, nothing worked. Only by the strength of his attention and by actively telling himself to let information slip away was he able to forget. It was as if the effort most of us use for remembering and the ease with which we forget were reversed for S.

We don't know the neural basis for S.'s remarkable memory. Perhaps he lacked the same sort of segregation most of us have between sensations in different sensory systems. This may have contributed to an uncommonly strong multimodal coding of memories. Maybe his synapses were more malleable than normal. Unfortunately, we'll never know.

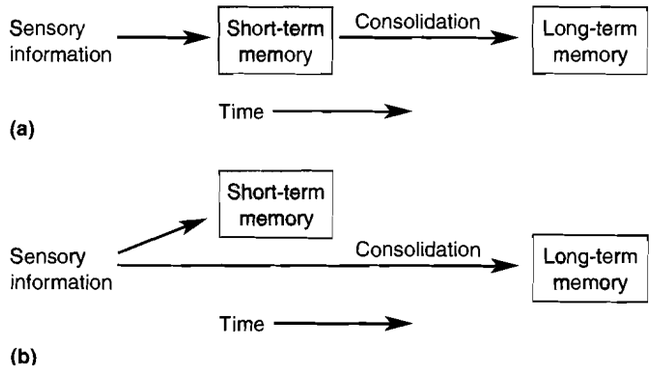

Figure 23.2
Short-term and long-term memory. Sensory information can be temporarily held in short-term memory, but permanent storage in long-term memory requires consolidation. **(a)** Information may be consolidated from short-term memory. **(b)** Alternatively, information processing necessary for consolidation may occur separately from short-term memory.

ple, short-term memory can be erased by head trauma or electroconvulsive shock. But the same treatments do not affect long-term memories (e.g., childhood memories), which were stored long ago. These observations have led to the idea that memories are stored in short-term memory and gradually converted into a permanent form via a process called **memory consolidation**. Memory consolidation, however, does not necessarily require short-term memory as an intermediary; the two types of memory may exist in parallel (Figure 23.2).

Short-term memory often requires holding information in mind. When someone tells you his or her phone number, you can retain it for a limited time by repeating the number to yourself. If the number is too long (e.g., a phone number with extra numbers for a foreign country), you may have trouble remembering it at all. Short-term memory is commonly studied by measuring a person's *digit span*, the maximum number of randomly chosen numbers a person can repeat after hearing a list read. The normal digit span is seven plus or minus two numbers.

Interestingly, there are reports of humans with cortical lesions who have normal short-term memory for information coming from one sensory system (e.g., they can remember as many written numbers as other people can) but a profound deficit when information comes from a different sense (e.g., they cannot remember more than one number spoken to them). These different digit spans in different modalities are consistent with the notion of multiple temporary storage areas in the brain.

Amnesia

As we all know, in daily life, forgetting is nearly as common as learning. But certain diseases and injuries to the brain cause **amnesia**, a serious loss of memory and/or the ability to learn. Concussion, chronic alcoholism, encephalitis, brain tumor, and stroke can all disrupt memory. You've probably seen a movie or television show in which a person undergoes a great trauma and wakes up the next day not knowing who he or she is and not remembering the past. That kind of absolute amnesia for past events and information is actually quite rare. It is more common for trauma to cause limited amnesia along with other nonmemory deficits. If amnesia is not accompanied by any other cognitive deficit, it is known as *dissociated amnesia* (i.e., the memory problems are dissociated from any other problems). We will focus on cases of dissociated amnesia because a clear relationship can be drawn between memory deficits and brain injury.

Following trauma to the brain, memory loss may manifest itself in two ways: retrograde amnesia and anterograde amnesia (Figure 23.3). **Retrograde amnesia** is characterized by memory loss for events prior to the

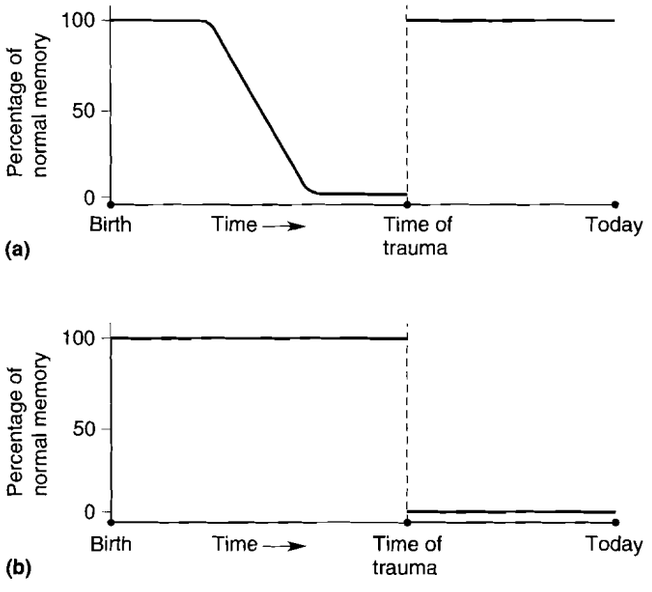

Figure 23.3
Amnesia produced by trauma to the brain. (a) In retrograde amnesia, events for a period prior to the trauma are forgotten, but memories from the distant past and the period following the trauma are intact. **(b)** In anterograde amnesia, events prior to the trauma can be remembered, but there are no memories for the period following the trauma.

trauma. In other words, you forget things you already knew. In severe cases, there may be complete amnesia for all declarative information learned before the trauma. More often, retrograde amnesia follows a pattern in which events in the months or years preceding the trauma are forgotten, but memory is increasingly strong for older memories. This is quite different from **anterograde amnesia**, the inability to form new memories following brain trauma. If the anterograde amnesia is severe, a person may be completely incapable of learning anything new. In milder cases, learning may be slower and require more repetition than normal. In clinical cases, there is often a mixture of retrograde and anterograde amnesias of different degrees of severity.

An example will help clarify. Consider the case of a 45-year-old man who had brain trauma at age 40. If he has severe retrograde amnesia, he cannot remember many things that occurred before the injury. If he has severe anterograde amnesia, he can remember nothing from age 40 until the present time.

A form of amnesia that involves a much shorter period is *transient global amnesia*. In this case, a sudden onset of anterograde amnesia lasts only for a period of minutes to days, accompanied by retrograde amnesia for recent events preceding the attack. This type of amnesia can result from brief cerebral ischemia, in which the blood supply to the brain is temporarily reduced, or concussion to the head from trauma, such as a car accident or a hard blow while playing football. There have been reports of transient global amnesia brought on by physical stress, drugs, cold showers, and even sex, presumably because all of these affect cerebral blood flow. Many cases have been linked to use of the antidiarrheal drug clioquinol (which has been taken off the market). In one case, a college student visiting Paris took clioquinol on the fifth day of a six-day holiday, during which she traveled with friends. When she got home, she discovered she couldn't remember her vacation at all! The memories for this short period were absent years later, but otherwise there was no lasting effect of the clioquinol. While we don't know exactly what causes transient global amnesia, it is probably a consequence of temporary blood deprivation to structures essential for learning and memory. Other forms of temporary amnesia can be caused by disease, brain trauma, and environmental toxins (Box 23.2).

Box 23.2

OF SPECIAL INTEREST

Forgettable Fish

Along the mid-Atlantic coast of the United States lurks a mysterious killer that has left millions of dead fish washed up on the shore. More sinister to humans, in the 1990s fishermen began to show up in doctors' offices with memory loss that was sometimes severe. The source of the trouble appears to be a unicellular microorganism called *Pfiesteria piscicida* and a number of its algal cousins. *Pfiesteria* is a dinoflagellate; at certain stages in its life cycle, it swims by means of a whiplike flagellum. *Pfiesteria* releases a neurotoxin that stuns fish, making them unable to escape. The dinoflagellates then swim to the fish and consume them.

Other dinoflagellates produce neurotoxins, but *Pfiesteria* is unusual in several ways. For example, the dinoflagellate *Gambierdiscus toxicus*, more commonly known as ciguatera, also produces a neurotoxin, ciguatoxin, that accumulates in fish that feed on coral reefs. Unlike *Pfiesteria*, however, ciguatera does not kill, and the fish continue to grow and are caught by fishermen. When the fish are consumed, the ciguatoxin binds to the Na^+ channels of people who eat the fish, increasing membrane excitability. Aside from nausea and diarrhea, the toxin produces a broad array of neurological symptoms, including numbness and tingling around the mouth, intense itching, and a reversal of the sensation of hot and cold.

Pfiesteria's modus operandi is different, as people do not become sick from ingesting the neurotoxin. Illness results from the seemingly innocuous activities of touching water containing the neurotoxin or inhaling it in the air. The fishermen, scientists, and others exposed to *Pfiesteria* experience a frightening array of neurological symptoms, including memory loss, difficulty concentrating, disorientation, and confusion. On visiting the doctor, patients tell of driving in the car and being unable to remember where they were going and what they were going to do. Some were even unable to remember their name or do simple arithmetic. The memory loss was sometimes so severe that it was confused with Alzheimer's disease. Fortunately, the symptoms generally subsided over the course of weeks or months after exposure to the toxin was stopped.

At present, the specific neurotoxins released by *Pfiesteria* that are responsible for the amnesia and other symptoms have not been isolated. Rats injected with solutions containing the neurotoxin have, however, been shown to have severe learning and memory impairment. Aside from identifying the toxin and the manner in which it attacks neurons is the question of why the sudden *Pfiesteria* outbreaks occur. The leading hypothesis is that water pollution from human sewage and fertilizers provided a rich source of food for the microbes, leading to tremendous growth in the *Pfiesteria* population.

THE SEARCH FOR THE ENGRAM

Now let's turn our attention to the parts of the brain that are involved in memory storage. The physical representation or location of a memory is called an **engram**, also known as a *memory trace*. When you learn the meaning of a word in French, where is this information stored—where is the engram? The technique most often used to answer this type of question is the time-honored experimental ablation method of Marie-Jean-Pierre Flourens (see Chapter 1).

Lashley's Studies of Maze Learning in Rats

In the 1920s, American psychologist Karl Lashley conducted experiments to study the effects of brain lesions on learning in rats. Well aware of the cytoarchitecture of the neocortex, Lashley set out to determine whether the engram resided in particular association areas of cortex (see Chapter 7), as was widely believed at the time.

In a typical experiment, he trained a rat to run through a maze to get a food reward (Figure 23.4a). On the first trial, the rat was slow getting to the food

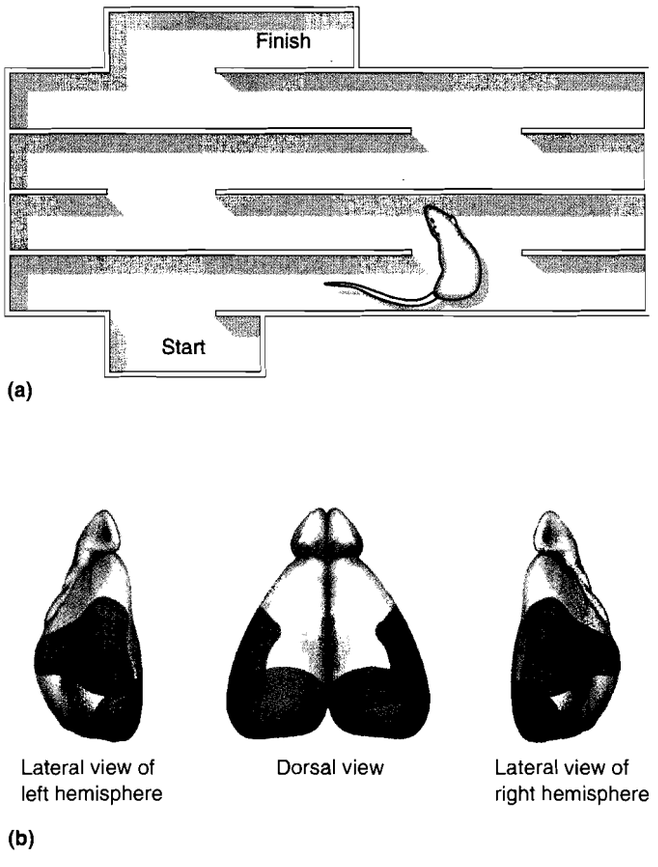

Figure 23.4
The effects of cortical lesions on maze performance. (a) The rat is trained to run through a maze from start to finish without entering blind alleys. **(b)** Three cortical lesions are shown in blue, yellow, and pink. **(c)** The greater the percentage of cortex destroyed, the more errors the rats make while they learn to run the maze. The number of errors shown is cumulative across trials, suggesting that rats with larger lesions had difficulty remembering which arms of the maze were blind alleys. (Source: Adapted from Lashley, 1929, Fig. 2, 16, and 23.)

because it would enter blind alleys and have to turn around. After running through the same maze repeatedly, the rat learned to avoid blind alleys and go straight to the food. Lashley was investigating how performance on this task was affected by lesions in the rat's cortex (Figure 23.4b). He found that rats given brain lesions before learning needed more trials to run the maze without going down blind alleys. The lesions seemed to interfere with their ability to learn.

In another group, a lesion was made after a rat had learned to run the maze without making mistakes. With the lesion, the rat made mistakes and went down blind alleys it had previously learned to avoid. It appeared that the lesion damaged or destroyed the memory for how to reach the food.

What was the effect of the size and location of the lesion? Interestingly, Lashley found that the severity of the deficits caused by the lesions (both learning and remembering) correlated with the *size* of the lesions (Figure 23.4c) but was apparently unrelated to the *location* of the lesion within the cortex. These findings led him to speculate that all cortical areas contribute equally to learning and memory; it is simply a matter of getting poorer performance on the maze task as the lesion gets bigger and the ability to remember the maze worsens. If true, this would be a very important finding because it implies that engrams are based on neural changes spread throughout the cortex rather than being localized to one area. The main problem with this interpretation is that it goes beyond what can safely be concluded from the data.

Notice how large the lesions are in Figure 23.4b. Perhaps one of the reasons Lashley did not find a difference in the effects of lesions at various locations is that his lesions were so large that they each damaged several cortical areas involved in learning the maze task. Another problem was that the rats might solve the maze in several different ways—by sight, feel, and smell—and the loss of one memory might be compensated for by another.

Subsequent research has proven Lashley's conclusions to be incorrect. All cortical areas do not contribute equally to memory. Nonetheless, he was correct that memories are distributed. Lashley had an important and lasting influence on the study of learning and memory because he led other scientists to consider ways in which memories might be distributed among the vast number of neurons of the cerebral cortex.

Hebb and the Cell Assembly

Lashley's most famous student was Donald Hebb, introduced in Chapter 22. Hebb reasoned that it was crucial to understand how external events are represented in the activity of the brain before one can hope to understand how and where these representations are stored. In a remarkable book published in 1949 entitled *The Organization of Behavior*, Hebb proposed that the internal representation of an object consists of all of the cortical cells that are activated by the external stimulus. Hebb called this group of simultaneously active neurons a **cell assembly** (Figure 23.5). Hebb imagined that all of these cells were reciprocally interconnected. The internal representation of the object was held in short-term memory as long as activity reverberated through the connections of the cell assembly. Hebb further hypothesized that if activation of the cell assembly persisted long enough, consolidation would occur by a "growth process" that made these reciprocal connections more effective (i.e., neurons that fired together would wire together; recall Hebb synapses from Chapter 22). Subsequently, if only a fraction of the cells of the assembly were activated by a later stimulus, as in Figure 23.5, the now-powerful reciprocal connections would cause the whole assembly to become active again, thus recalling the entire internal representation of the external stimulus—in this case, a circle.

Hebb's important message was that the engram (1) could be widely distributed among the connections that link the cells of the assembly and (2) could include the same neurons that are involved in sensation and perception. Destruction of only a fraction of the cells of the assembly would not be expected to eliminate the memory, which may explain Lashley's results. Hebb's ideas stimulated the development of neural network computer models. Although his original assumptions had to be modified slightly, these

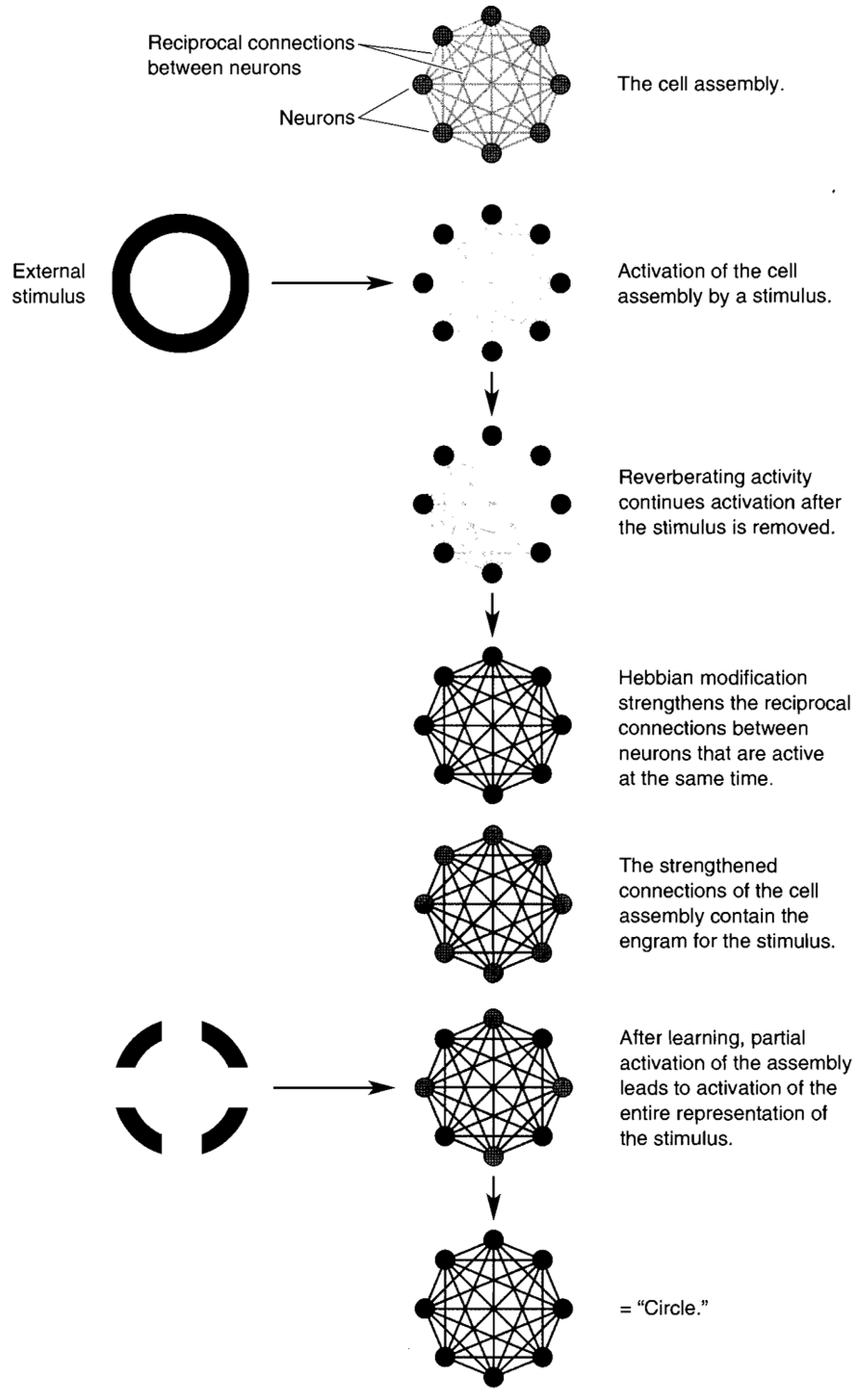

Figure 23.5
Hebb's cell assembly and memory storage.

models have successfully reproduced many features of human memory (Box 23.3).

Localization of Declarative Memories in the Neocortex

According to Hebb, if an engram is based on information from only one sensory modality, it should be possible to localize it within the regions of cortex that serve this modality. For example, if the engram relies only on visual in-

Box 23.3

BRAIN FOOD

A Model of a Distributed Memory

Historically, most of the progress in neuroscience research has come from experimental studies. But today, theoretical neuroscience is playing an increasing role, and the use of computational models of neural systems is widespread. In some cases, a model can provide insights into the workings of a system that are otherwise hard to gain. One area in which models have been helpful is the study of systems for learning and memory. Let's look at a model for distributed memory storage.

To keep things simple, we'll examine a nervous system consisting of three sensory neurons (the inputs) and three postsynaptic neurons (the outputs). The inputs will represent patterns of activity in visual afferents in response to the faces of three people, Eric, Kyle, and Kenny. Ignoring the complexities of visual processing, we'll assume each of these three inputs excites all three output neurons—A, B, and C (Figure A, part a). Before the system learns who Eric, Kyle, and Kenny are, each of the three output cells responds at roughly the same level to each of the inputs (Figure A, part b). There is no way to tell from the outputs of cells A, B, and C which face was the stimulus at a given time.

Now let's imagine that after being exposed to the three inputs repeatedly, the synaptic effectiveness, or strength, changes. One possibility is that after learning, Eric's face activates only cell A, Kyle's face activates only cell B, and Kenny's face activates only cell C (Figure A, part c). We can reliably tell which face is present at any time by looking to see which output neuron is active. All of the relevant information that allows the system to recognize the face—the memory—is stored in the synaptic weights. Part c represents a nondistributed memory because all of the information about Eric, for example, is stored in the single synapse with output cell A. The system can recognize that Eric is present without even bothering to look at the outputs of cells B and C.

In an alternative system, learning the three faces would again alter the synaptic weights, but none of them would be zero (Figure A, part d). The synaptic changes that store the memories can make the inputs more or less effective; memory formation does not involve only increases in synaptic strength. This is a *distributed memory* system because the memory of each face is stored in three synapses. In a real nervous system, many thousands of synapses may be involved. Recognition of one of the input faces requires comparing the strength of activity across all of the output neurons—the memory is "distributed." One reason the distributed system seems more realistic is that recordings from cortical neurons do not suggest individual neurons are specifically responsive to every image we recognize. Presumably, human recognition is based on the relative activation of thousands of neurons.

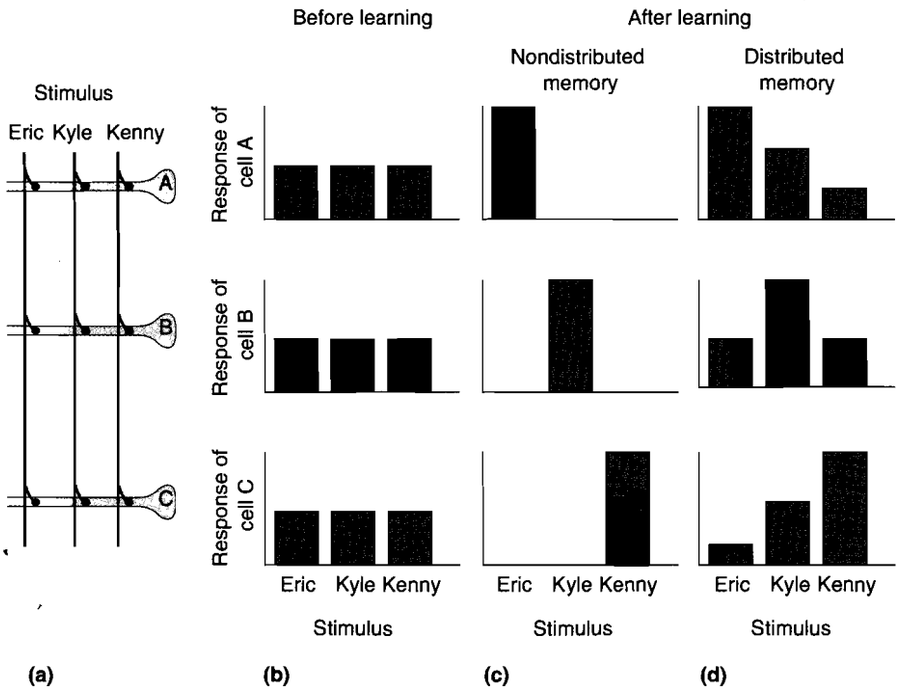

Figure A

An attractive feature of the distributed memory system is its relative immunity to catastrophic memory loss if output neurons die. In the nondistributed scheme, recognition of Kenny totally depends on the response of cell C. If this cell dies, say goodbye to Kenny. Contrast this with the distributed system. If cell B is lost, we can still recognize Kyle by comparing the responses of cells A and C. The more neurons and synapses that are involved in the distributed memory, the lower the consequence of losing any single cell. This relative immunity to the effects of cell loss is a great advantage. Neurons in the human brain die every day, and it is probably because of the distributed nature of memory that we don't suddenly lose memories for people and events.

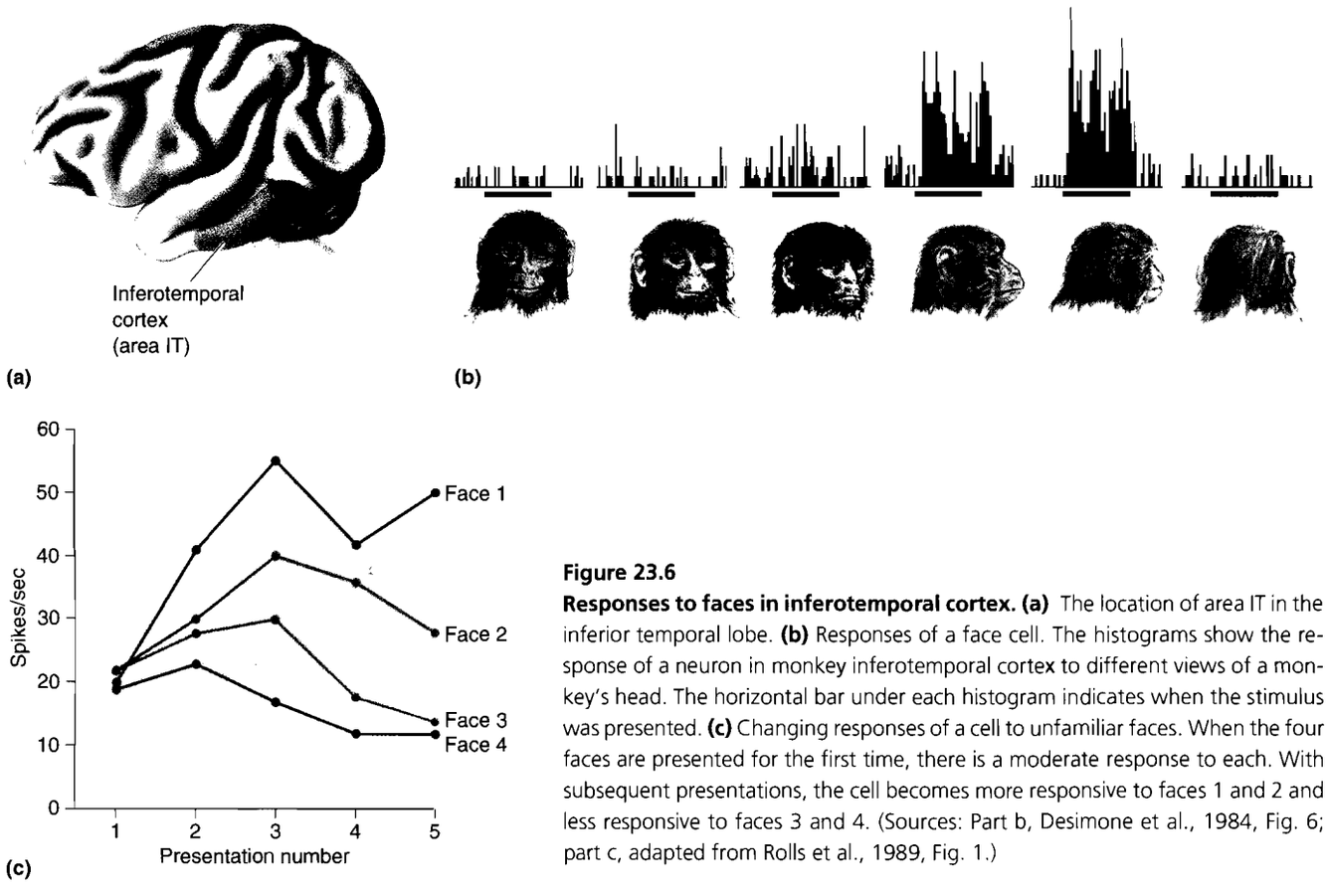

Figure 23.6
Responses to faces in inferotemporal cortex. (a) The location of area IT in the inferior temporal lobe. **(b)** Responses of a face cell. The histograms show the response of a neuron in monkey inferotemporal cortex to different views of a monkey's head. The horizontal bar under each histogram indicates when the stimulus was presented. **(c)** Changing responses of a cell to unfamiliar faces. When the four faces are presented for the first time, there is a moderate response to each. With subsequent presentations, the cell becomes more responsive to faces 1 and 2 and less responsive to faces 3 and 4. (Sources: Part b, Desimone et al., 1984, Fig. 6; part c, adapted from Rolls et al., 1989, Fig. 1.)

formation, then we expect it to reside within the visual cortex. Studies of visual discrimination in monkeys are consistent with this proposal.

Studies in Monkeys. Macaque monkeys can be trained to perform visual discriminations (e.g., they can differentiate pairs of objects based on their shapes and learn to associate one with a food reward). After being trained on this task and becoming proficient at it, a lesion is made in inferotemporal cortex (area IT), a high-order visual area in the inferior temporal lobe (Figure 23.6a). With this brain lesion, the animal can no longer perform the discrimination task, even though its basic visual capacities remain intact. It appears as if the animal no longer remembers the stimulus shape associated with the reward. As in Lashley's experiments, the implication is that the memory for the task is stored in the cortex. In the case of a task specific to vision, however, the memory appears to be stored in a high-order visual area. Stated another way, inferotemporal cortex is both a visual area and an area of memory storage.

Further evidence that inferotemporal cortex is involved in certain types of memory storage comes from physiological experiments in which the response properties of individual neurons are examined. For example, recordings made from IT neurons suggest that they may encode memories of faces (Figure 23.6b). In a typical experiment, the monkey is alert, and an electrode is used to record from an IT neuron. Initially, the response of the neuron to multiple presentations of familiar faces (other monkeys the subject frequently sees) is recorded. The face cell responds more to some faces than to others. When new faces unfamiliar to the monkey are introduced, interesting neuronal responses result, as shown in Figure 23.6c. The first time new faces

are seen, the cell responds at about the same moderate level to all of them. With a couple of additional exposures, however, the response changes such that some faces evoke a significantly greater response than others do. The cell is becoming selective in its response to these new stimuli as we watch it. With continued presentation of the same group of faces, the response of the neuron to each pattern becomes more stable. We can speculate that the response selectivity of this neuron and others is part of a distributed code for the representation—the memory—of many faces. This dynamic aspect of responses in area IT supports Hebb's view that the brain can use cortical areas for both the processing of sensory information and the storage of memories.

Studies in Humans. When we discussed visual processing beyond striate cortex in Chapter 10, we saw, from functional magnetic resonance imaging (fMRI) studies in humans, results that indicate a small portion of the brain is particularly activated by faces. Other fMRI experiments have shown responses specific to a range of types of objects. For example, in one study, subjects were presented with various pictures of birds and cars. Everyone can recognize a few bird species or car models, but bird-watchers and car buffs are experts at discriminating the subtleties. When bird experts and car experts view pictures of both birds and cars, the brain responses are different. The bird experts have areas of extrastriate visual cortex that are significantly more activated by images of birds than by other objects, such as cars. Conversely, car experts show an especially strong response to pictures of cars (Figure 23.7).

The meaning of these activity patterns is hotly debated. One possibility is that the different activity patterns in the two types of experts reflect highly developed specialized processing of visual features needed to classify particular examples. Obviously, birds and cars differ in many ways—feathers, sheet metal, and so on. Another interpretation is that extrastriate visual areas encode memories for birds or cars (or even faces, as we saw in Chapter 10). Rather than focusing on the uncertainty about whether the responses in this type of experiment are sensory or memory, we note that the results are in line with Hebb's idea that the same area of cortex can subserve both functions.

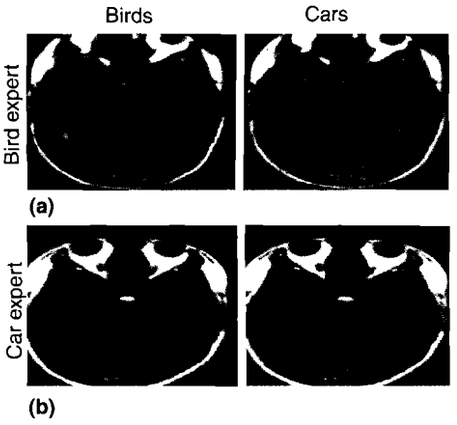

Figure 23.7
Functional MRI recordings of brain activity in bird and car experts. (a) Bird experts showed greater activity (red) in extrastriate visual areas in response to birds than other objects. **(b)** Extrastriate cortex in car experts was more activated by images of cars. (Source: Gauthier et al., 2000.)

Electrical Stimulation of the Human Temporal Lobes

One of the most intriguing and controversial studies implicating the neocortex of the temporal lobe in the storage of declarative memory traces involved electrical stimulation of the human brain. In Chapters 12 and 14, we discussed the work of Wilder Penfield in which patients, as part of surgical treatment for severe epilepsy, had their brain electrically stimulated at numerous locations prior to ablation of the seizure-prone region. Stimulation of somatic sensory cortex caused the patient to feel tingling in regions of skin, whereas stimulation of motor cortex caused a certain muscle to twitch.

Electrical stimulation of the temporal lobe occasionally produced more complex sensations than those obtained with stimulation in other brain areas. In a number of cases, Penfield's patients described sensations that sounded like hallucinations or recollections of past experiences. This is consistent with reports that epileptic seizures of the temporal lobes can evoke complex sensations, behaviors, and memories. Here is part of Penfield's account of one operation:

At the time of operation, stimulation of a point on the anterior part of the first temporal convolution on the right caused him [the patient] to say, "I feel as though I were in the bathroom at school." Five minutes later, after negative stimulations elsewhere, the electrode was reapplied near the same point. The patient then said something about "street corner." The surgeon asked him, "where" and he replied,

"South Bend, Indiana, corner of Jacob and Washington." When asked to explain, he said he seemed to be looking at himself—at a younger age.

(Penfield, 1958, p. 25)

Another patient reported similar flashbacks. When her temporal cortex was stimulated, she said, "I think I heard a mother calling her little boy somewhere. It seemed to be something that happened years ago." With stimulation at another location, she said, "Yes, I hear voices. It is late at night around the carnival somewhere—some sort of traveling circus. . . . I just saw lots of big wagons that they use to haul animals in."

Are these people reexperiencing events from earlier in their life because memories are evoked by the electrical stimulation? Does this mean that memories are stored in the neocortex of the temporal lobe? Those are tough questions. One interpretation is that the sensations are recollections of past events. That such elaborate sensations were obtained only when the temporal lobe was stimulated suggests that the temporal lobe may play a special role in memory storage. Other aspects of the findings, however, do not clearly support the hypothesis that engrams are being electrically activated. For instance, in some of the cases in which the stimulated part of the temporal lobe was removed, the memories that had been evoked by stimulation in that area could be evoked by stimulation somewhere else. In other words, the memory had not been "cut out." Also, it is important to appreciate that complex sensations were reported by only a minority of the patients, and all of these patients had abnormal cortex associated with their epilepsy.

There is no way to prove with certainty whether the complex sensations evoked by temporal lobe stimulation are recalled memories. Clearly, however, the consequences of temporal lobe stimulation and temporal lobe seizures can be qualitatively different from stimulation of other areas of the neocortex. We will next take a closer look at the structure of the temporal lobes and the elements within them that are strongly implicated in learning and memory.

THE TEMPORAL LOBES AND DECLARATIVE MEMORY

The temporal lobe lies under the temporal bone, so named because the hair of the temples is often the first to go gray with the passage of time (*tempus* is Latin for "time"). The association of the temporal lobe with time was fortuitous, in that considerable evidence points to this region of the brain as being particularly important for the recording of past events. The temporal lobes contain the temporal neocortex, which may be a site of long-term memory storage. Also within the temporal lobe are the hippocampus and other structures, which are critical for the formation of declarative memories.

The Effects of Temporal Lobectomy

If the temporal lobe is particularly important for learning and memory, one would expect removing both temporal lobes to have a profound effect on these functions. Recall from the discussion of the Klüver-Bucy syndrome in Chapter 18 that bilateral temporal lobectomy does seem to have some effect on memory. The monkeys with temporal lobectomy that Klüver and Bucy studied had a peculiar way of interacting with their environment in addition to a host of other abnormalities. The monkeys explored their room by placing objects in their mouth. If an object was edible, they would eat it; if it wasn't, they would drop it. Their behavior suggested, however, that they did not have basic perceptual deficits. In the words of Klüver and Bucy, they exhib-

ited "psychic blindness"—even though they could see things, they did not appear to understand with their eyes what the objects were. They would repeatedly go back to the same inedible objects, put them in their mouth, then toss them aside. This problem with object recognition is probably related to memory function in the temporal lobe.

A Human Case Study: H. M. A renowned case of amnesia resulting from temporal lobe damage provides further evidence for the importance of this region in memory. A man known by his initials, H. M., has been extensively studied. H. M. had minor epileptic seizures beginning around age 10, and as he aged, they became more serious generalized seizures involving convulsions, tongue biting, and loss of consciousness. Although the cause of the seizures is not known, they may have resulted from damage sustained in an accident in which he was knocked off his bicycle at age 9 and lay unconscious for 5 minutes. After graduating from high school he got a job, but despite heavy medication with anticonvulsants, his seizures increased in frequency and severity to the point that he was unable to work. In 1953, at age 27, H. M. had an operation in which an 8 cm length of medial temporal lobe was bilaterally excised, including cortex, the underlying amygdala, and the anterior two-thirds of the hippocampus, in a last-ditch attempt to assuage the seizures (Figure 23.8). The surgery was successful in alleviating the seizures.

The removal of much of the temporal lobes had little effect on H. M.'s perception, intelligence, or personality. H. M. is still alive, and in nearly every way, he appears to be normal. This normal appearance, however, belies the reality that the surgery left him with amnesia so profound that he is incapable of performing basic human activities. H. M. has partial retrograde amnesia for the years preceding the operation. Much more serious, however, is his extreme anterograde amnesia. While he can remember a great deal about his childhood, he is unable to remember someone he met 5 minutes earlier. Dr. Brenda Milner of the Montreal Neurological Institute has worked with H. M. for more than 40 years, but she has to introduce herself to him every time they meet (Box 23.4). Milner has said it appears that H. M. forgets events as quickly as they occur. If he is told to remember a number and is then distracted, he not only forgets the number, he also forgets that he was asked to remember one. H. M. does not live in the same home he did in 1953, so he cannot find his way around his own neighborhood. He always underestimates his age, and he is unable to recognize a current picture of himself.

To be clear about the nature of H. M.'s amnesia, we must contrast what was lost with what is retained. He remembers his childhood, so long-term memories formed before the surgery and his ability to recollect past events were not destroyed. His short-term memory is also normal. For instance, with constant rehearsal he can remember a list of six numbers, although any interruption will cause him to forget. He simply has an extreme inability to form new declarative memories. Importantly, he is able to learn new tasks (i.e., form new *procedural* memories). For example, he was taught to draw by looking at his hand in a mirror, a task that takes a good deal of practice for anyone. The odd thing is that he has learned to perform new tasks, despite the fact that he has no recollection of the specific experiences in which he was taught to do them (the declarative component of the learning).

The characteristics of H. M.'s amnesia reinforce the idea that the neuroanatomy and neural mechanisms underlying procedural and declarative memory and short-term and long-term memory are not the same. In our search to understand the role of the medial temporal lobe in learning and memory, we are led to focus on the processing and consolidation of new declarative memories.

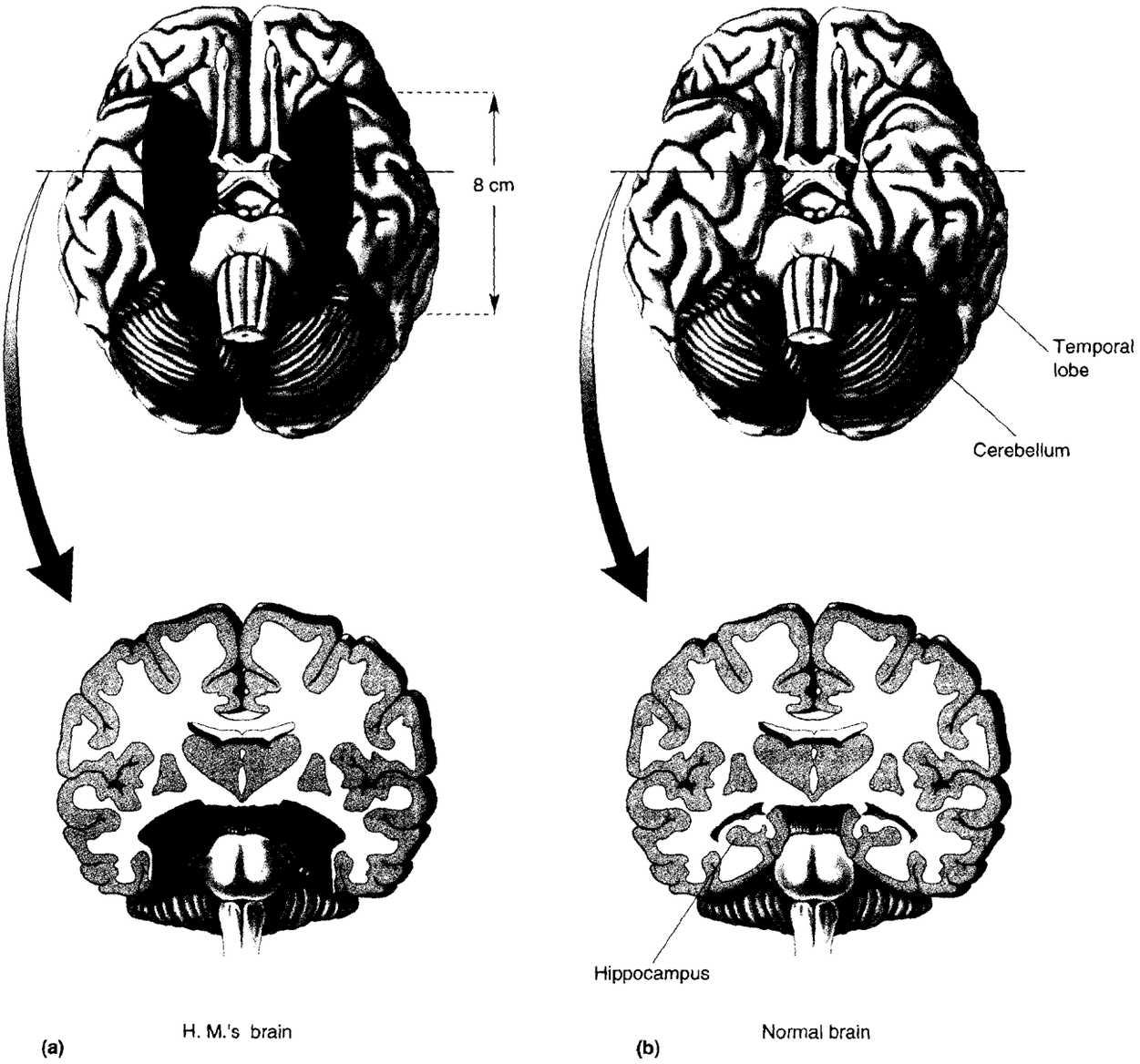

Figure 23.8
The brain lesion in patient H. M. that produced severe anterograde amnesia. (a) The medial temporal lobe was removed from both hemispheres in H. M.'s brain to alleviate severe epileptic seizures. **(b)** A normal brain showing the location of the hippocampus and cortex that were removed from H. M.'s brain. (Source: Adapted from Scoville and Milner, 1957, Fig. 2.)

The Medial Temporal Lobes and Memory Processing

In the medial temporal lobe, a group of interconnected structures appears to be of great importance for declarative memory consolidation. The key structures are the hippocampus, the nearby cortical areas, and the pathways that connect these structures with other parts of the brain (Figure 23.9). As we saw in Chapter 7, the **hippocampus** is a folded structure situated medial to the lateral ventricle. Ventral to the hippocampus are three important cortical regions that surround the rhinal sulcus: the **entorhinal cortex**, which occupies the medial bank of the rhinal sulcus; the **perirhinal cortex**, which occupies the lateral bank; and the **parahippocampal cortex**, which lies lateral to the

Box 23.4

PATH OF DISCOVERY

Discovering Memory in the Medial Temporal Lobe With H. M.

BY BRENDA MILNER

There was nothing in my background to predict a career in science. My parents' life was dominated by music, and it was a bitter disappointment that I had no musical aptitude. Instead, I studied psychology and eventually became a graduate student under Donald Hebb at McGill University. My research on the effects of temporal lobe lesions was conducted with patients who had undergone brain surgery for the relief of epilepsy. I was impressed, as no one could fail to be, by the experience of being present in the gallery of the operating room while Wilder Penfield stimulated the exposed cortex in awake patients and elicited reports of complex hallucinatory experiences. Penfield was convinced that he had excited part of the neural substrate of past experience conceived by him as a continuous record. To me, as an experimental psychologist, this tape recorder notion of memory seemed implausible.

Because most of Penfield's operations, which were in one hemisphere only, caused little behavioral change, we were shocked to discover that in two of the patients, unilateral resection of the medial structures of the temporal lobe led to severe anterograde amnesia. We hypothesized that in each case there had been a preexisting but preoperatively undetected atrophic lesion in the unoperated hemisphere. We were subsequently contacted by the neurosurgeon William Scoville, who said he had seen a similar memory disturbance in a patient on whom he had performed a bilateral medial temporal lobe resection. This was patient H. M., who is now very well known. Penfield asked me if I would like to go down to Hartford to study the patient, and that's how it started.

H. M.'s life had been totally disrupted by serious epileptic seizures. Prior to Scoville's surgery, he was on near-toxic doses of all kinds of medication. His graduation from high school came very late. He couldn't keep a job. He had no social life; he had nothing.

Removal of the medial temporal lobe didn't affect H. M.'s reasoning ability, his ability to repeat a short series of digits, or any such tasks. Incredibly, I found that he could retain a three-digit number for at least 15 minutes by continuous rehearsal, combining and recombining the digits according to an elaborate mnemonic scheme. Only when H. M. puts something out of his mind and turns to something else is the first thing lost. Say I had been working with him all morning, just the two of us, and then I'd go out for lunch. I would come back and walk by H. M. in the waiting room, and he would have no recognition of me, even though he is a very polite man. Such results appear to support the distinction between a primary memory process with a rapid decay and an overlapping secondary process (impaired in H. M.) by which the long-term storage of information is achieved.

Brenda Milner

To my surprise, H. M. had no trouble learning a mirror-drawing task I administered. Although his learning was normal, at the end of the last trial he had no idea that he had ever performed the task before. This was learning without any sense of familiarity. Nowadays we are well aware that such dissociations are possible following a discrete brain lesion, but for me at the time, it was quite astonishing. It was also early evidence of the existence of more than one memory system in the brain.

Our findings with H. M. had a mixed reception during that period, largely because monkeys with similar bilateral lesions performed normally on visual discrimination learning tasks. An important breakthrough came in 1978, when Mortimer Mishkin demonstrated a severe deficit in monkeys with bilateral medial temporal lobe lesions on a one-trial task of object recognition memory. This is, of course, what we should have predicted from H. M.'s failure on single-trial, nonverbal delayed matching tasks. It was a real discovery—the reason the monkeys with lesions exactly like H. M.'s had apparently succeeded where H. M. had failed was that they were learning the task in a different way, as a procedure over hundreds of trials.

As I look back over the past 50 years, it seems to me that I have had a lot of luck in being in the right place at the right time but also enough tenacity of purpose not to be discouraged when the going got rough. I am also grateful for my curiosity, which led me to wish to delve deeper into phenomena that caught my eye and which keeps me going to this day.

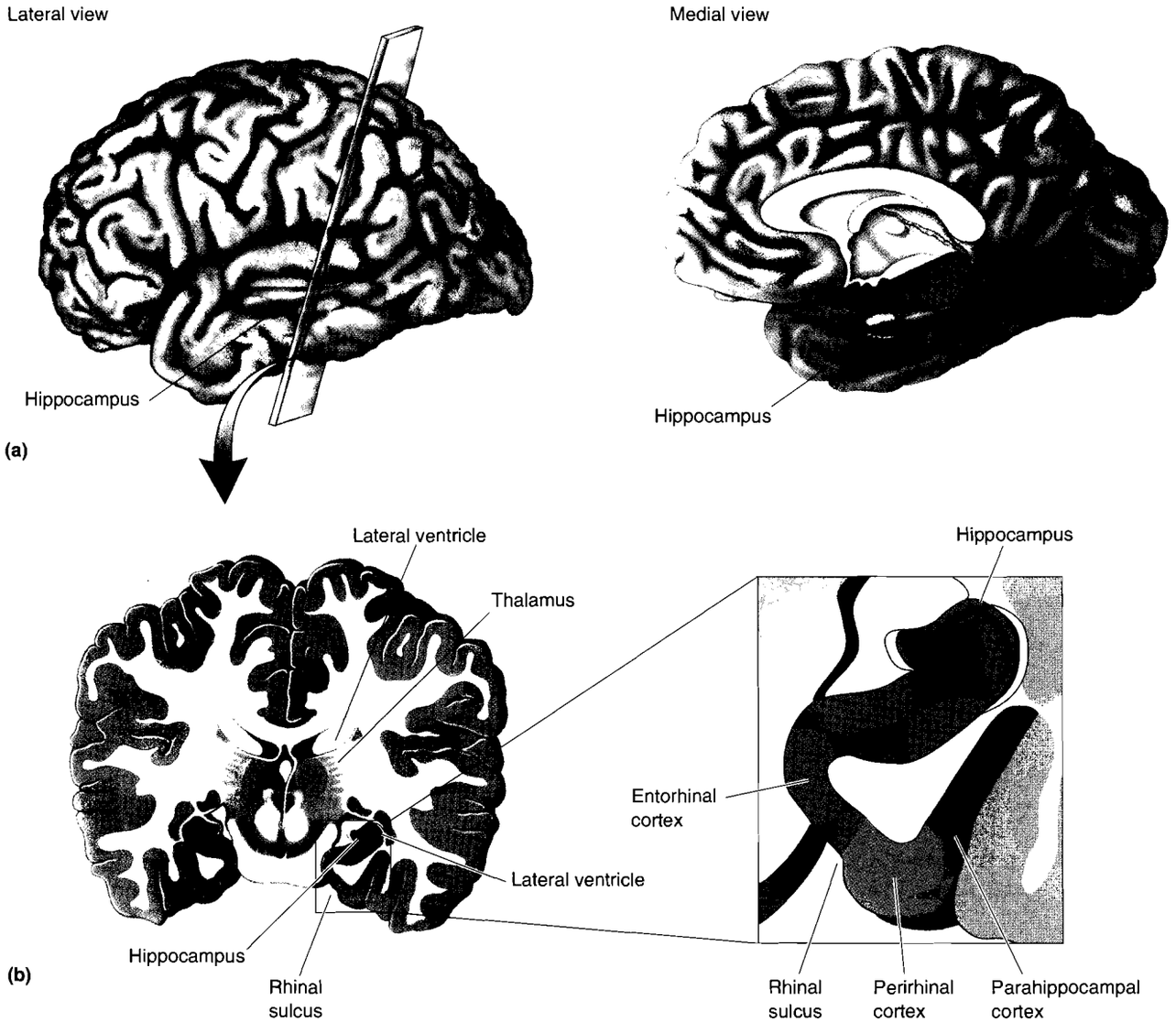

Figure 23.9
Structures in the medial temporal lobe involved in declarative memory formation. (a) Lateral and medial views show the location of the hippocampus in the temporal lobe. **(b)** The brain is sectioned coronally to show the hippocampus and cortex of the medial temporal lobe.

rhinal sulcus. (We'll refer to entorhinal cortex and perirhinal cortex collectively as rhinal cortex.)

Inputs to the medial temporal lobe come from the association areas of the cerebral cortex, containing highly processed information from all sensory modalities (Figure 23.10). For instance, inferotemporal visual cortex projects to the medial temporal lobe, but low-order visual areas such as striate cortex do not. This means that the input contains complex representations, perhaps of behaviorally important sensory information, rather than responses to simple features such as light-dark borders. Input first reaches the rhinal and parahippocampal cortex before being passed to the hippocampus. A major output pathway from the hippocampus is the **fornix**, which loops around the thalamus before terminating in the hypothalamus.

An Animal Model of Human Amnesia. The effects of temporal lobectomy, particularly the amnesia of H. M., make a strong case that one or more struc-

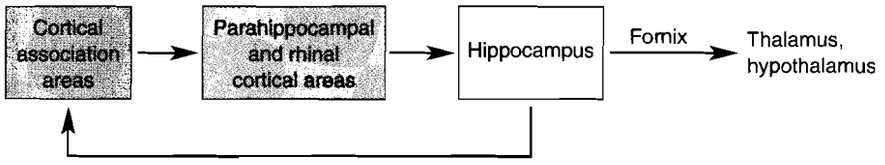

Figure 23.10
Information flow through the medial temporal lobe.

tures in the medial temporal lobe are essential for the formation of declarative memories. If these structures are damaged, severe anterograde amnesia results. There has been intensive investigation into the particular structures in the medial temporal lobe that are essential for memory formation. For the most part, these studies use the experimental ablation technique to assess whether the removal of some part of the temporal lobe affects memory.

Because the macaque monkey brain is similar in many ways to the human brain, macaques are frequently studied to further our understanding of human amnesia. The monkeys are most often trained to perform a task called **delayed non-match to sample (DNMS)** (Figure 23.11). In this type of experiment, a monkey faces a table that has several small wells in its surface. It first sees the table with one object on it covering a well. The object may be a wooden block or a chalkboard eraser (the sample stimulus). The monkey is trained to displace the object so that it can get a food reward in the well under the object. After the monkey gets the food, a screen is put down to prevent the monkey from seeing the table for some period (the delay interval). Finally, the animal gets to see the table again, but now there are two objects on it: One is the same as before, and another is new. The monkey's task is to displace the new object (the non-matching object) to get another food reward in a well below it. Normal monkeys are relatively easy to train on the non-matching task and get very good at it, probably because it exploits their natural curiosity for novel objects. With delays between the two stimulus presentations of anywhere from a few seconds to 10 minutes, the monkey

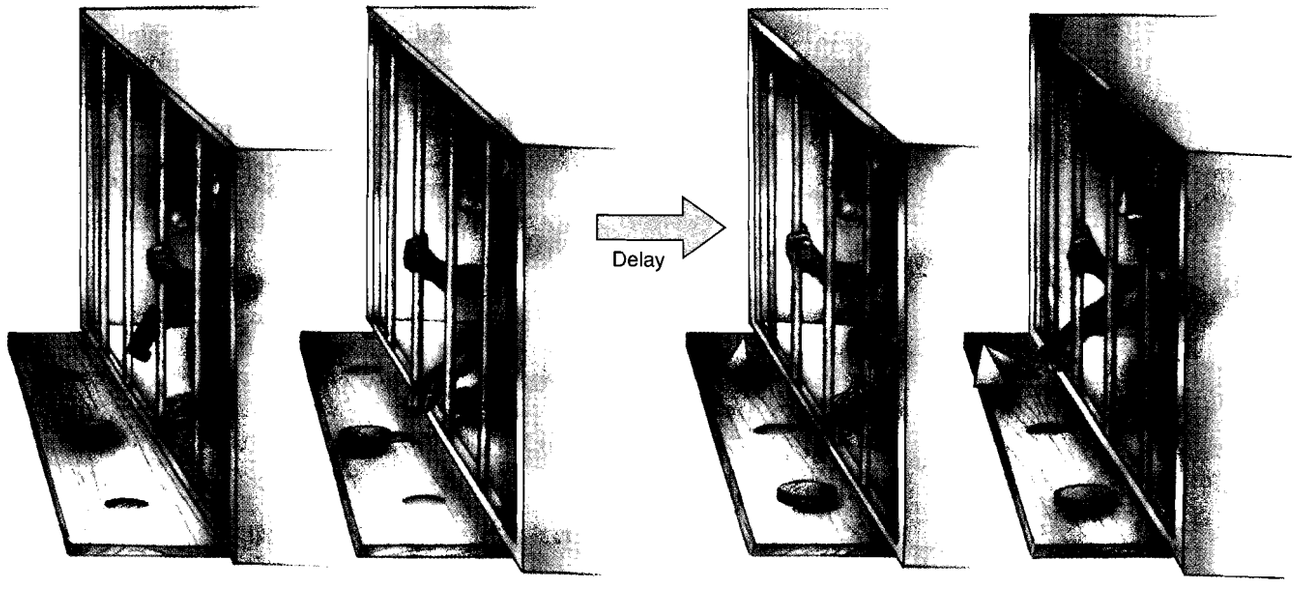

Figure 23.11
The DNMS task. A monkey first displaces a sample object to obtain a food reward. After a delay, two objects are shown, and recognition memory is tested by having the animal choose the object that does not match the sample. (Source: Adapted from Mishkin and Appenzeller, 1987, p. 6.)

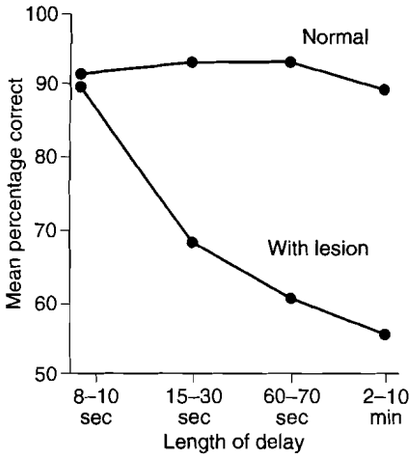

Figure 23.12
The effect of medial temporal lesions on DNMS performance. The Y axis shows the percentage of correct choices made by monkeys as a function of the length of the delay interval. The performance of normal monkeys is compared with that of monkeys with large bilateral medial temporal lesions. (Source: Adapted from Squire, 1987, Fig. 49.)

correctly displaces the non-matching stimulus on about 90% of the trials. Memory required in the DNMS task has been called **recognition memory** because it involves the ability to judge whether a stimulus has been seen before. It is probably reasonable to assume that if the animal can perform this task with a delay several minutes long, it must have formed a long-term memory for the sample object.

In the early 1980s, experiments performed by Mortimer Mishkin and his colleagues at the National Institute of Mental Health and Larry Squire and his coworkers at the University of California, San Diego, demonstrated that severe deficits on the DNMS task result from bilateral medial temporal lesions in macaque monkeys. Performance was close to normal if the delay between the sample stimulus and the two test stimuli was short (a few seconds). This is very important because it indicates that the monkey's perception was still intact after the ablation and it remembered the DNMS procedure. But when the delay was increased from a few seconds to a few minutes, the monkey made more and more errors choosing the non-matching stimulus (Figure 23.12). With the lesion, the animal was no longer as good at remembering what the sample stimulus was in order to choose the other object. Its behavior suggests that it forgot the sample stimulus if the delay was too long. The deficit in recognition memory produced by the lesion was not modality specific, since this deficit was also observed if the monkey was allowed to touch but not see the objects.

The monkeys with medial temporal lesions appeared to provide a good model of human amnesia. As with H. M., the amnesia involved declarative rather than procedural memory, it seemed more anterograde than retrograde, and long-term memory was more severely impaired than short-term memory. Note that the lesions that were originally found to produce recognition memory deficits in monkeys were quite large. They included the hippocampus, amygdala, and rhinal cortex. At one time it was thought that the key structures damaged in the lesions were the hippocampus and amygdala. It has now been shown, however, that selective amygdala lesions have no effect on this form of memory and lesions of the hippocampus alone produce only relatively mild amnesia. For example, Squire studied a man known by the initials R. B. who had bilateral hippocampal damage as a result of oxygen deprivation during surgery. Although R. B. clearly had difficulty forming new memories, this anterograde amnesia was not nearly as severe as that seen in H. M. The most severe memory deficits result from damage to the perirhinal cortex.

Together with the hippocampus, the cortex in and around the rhinal sulcus evidently performs a critical transformation of the information coming from association cortex. One hypothesis is that these medial temporal structures consolidate the memory into cortex. It is also possible, however, that they serve as an essential intermediate processing stage that involves something other than consolidation. These cortical regions may also do something else. In H. M. and possibly in R. B., there was some retrograde amnesia. Perhaps the cortex of the medial temporal lobes stores memories temporarily before they are ultimately transferred to the neocortex elsewhere for more permanent storage.

The Diencephalon and Memory Processing

Lesions in the medial temporal lobe can produce profound amnesia, but other lesions can also disrupt memory. Outside the temporal lobe, one of the brain regions most associated with memory and amnesia is the diencephalon.

The three regions of the diencephalon implicated in the processing of recognition memory are the anterior and dorsomedial nuclei in the thalamus

and the mammillary bodies in the hypothalamus. Recall that a major output of the hippocampal formation is a bundle of axons making up the fornix. Most of these axons project to the mammillary bodies (Figure 23.13). Neurons in the mammillary bodies project to the anterior nucleus of the thalamus. This circuit from hippocampus to hypothalamus to anterior nucleus and then to cingulate cortex should sound familiar; it is half of the Papez circuit we discussed in Chapter 18. The dorsomedial nucleus of the thalamus also receives input from temporal lobe structures, including the amygdala and inferotemporal neocortex, and it projects to virtually all of frontal cortex.

Large midline thalamic lesions in monkeys produce relatively severe deficits on the DNMS task. These lesions damage the anterior and dorsomedial nuclei of the thalamus, producing retrograde degeneration in the mammillary bodies. Bilateral lesions limited to either the dorsomedial nuclei or the anterior nuclei produce significant but milder deficits. The limited data available suggest that rather mild deficits are seen after lesions in only the mammillary bodies.

A Human Case Study: N. A. Reports for many years have suggested a relationship between human amnesia and damage to the diencephalon. A particularly dramatic example is the case of a man known as N. A. In 1959, at age 21, N. A. was a radar technician in the U. S. Air Force. One day he was sitting down assembling a model in his barracks while behind him a roommate played with a miniature fencing foil. N. A. turned at the wrong moment and was stabbed. The foil went through his right nostril, taking a leftward course into his brain. Many years later, when computed tomography was performed, the only obvious damage was a lesion in his left dorsomedial thalamus, though there may have been other damage.

After his recovery, N. A.'s cognitive ability was normal but his memory was impaired. He had retrograde amnesia of about 2 years and relatively severe anterograde amnesia. While he could remember some faces and events

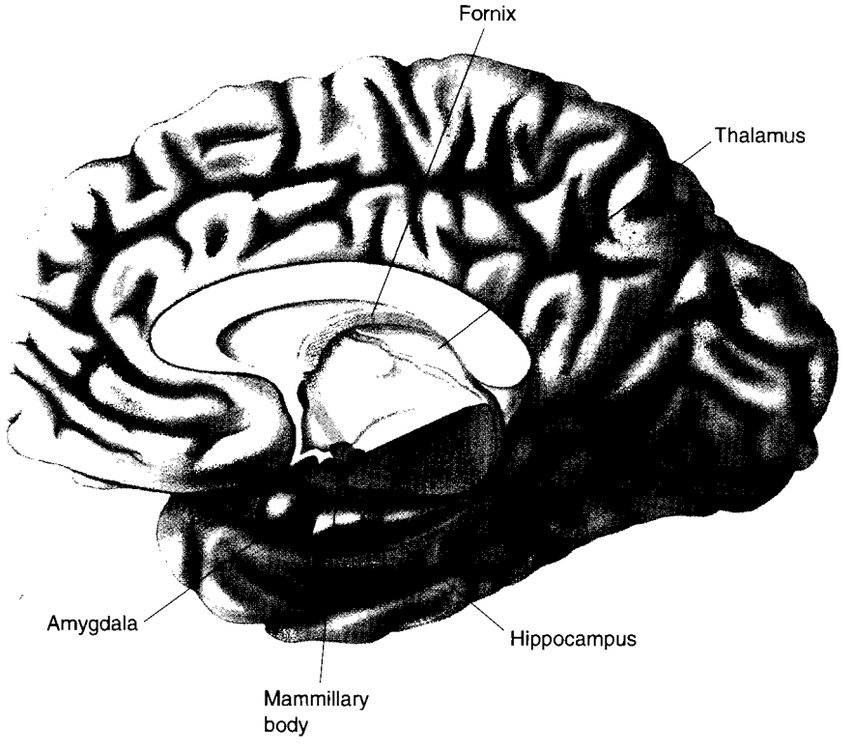

Figure 23.13
Components of the diencephalon involved in memory. The thalamus and mammillary bodies receive afferents from structures in the medial temporal lobe.

from the years following his accident, even these memories were sketchy. He had difficulty watching television because during commercials he'd forget what was happening on the show. In a sense, he lived in the past by preferring to wear old familiar clothes and keeping his hair in a crewcut.

Although N. A.'s amnesia was less severe than H. M.'s, the quality was strikingly similar. There was preservation of short-term memory, recollection of old memories, and general intelligence. Along with difficulty forming new declarative memories, he had retrograde amnesia for years preceding the accident that produced the amnesia. The similarities in the effects of medial temporal and diencephalic lesions suggest that these interconnected areas are part of a system serving the common function of memory consolidation.

Korsakoff's Syndrome. Further support for a role of the diencephalon in memory comes from Korsakoff's syndrome. Usually resulting from chronic alcoholism, **Korsakoff's syndrome** is characterized by confusion, confabulations, severe memory impairment, and apathy. As a result of poor nutrition, alcoholics may develop a thiamin deficiency, which can lead to such symptoms as abnormal eye movements, loss of coordination, and tremors. This condition can be treated with supplemental thiamin. If left untreated, thiamin deficiency can lead to structural brain damage, which does not respond to thiamin treatment. The structural damage produces Korsakoff's syndrome. Although not all cases of Korsakoff's syndrome are associated with damage to the same parts of the brain, there are usually lesions in the dorsomedial thalamus and the mammillary bodies.

In addition to anterograde amnesia, Korsakoff's syndrome can involve more severe retrograde amnesia than observed in N. A. and H. M. There is no strong correlation between the severity of anterograde amnesia and retrograde amnesia in Korsakoff's syndrome. This is consistent with the other studies of amnesia we've discussed, suggesting that the mechanisms involved in consolidation (disrupted in anterograde amnesia) are largely distinct from processes used to recall memories (disrupted in retrograde amnesia). Based on a small number of cases such as that of N. A., researchers suspect that anterograde amnesia associated with diencephalic lesions results from damage to the thalamus and mammillary bodies. Although it is not clear which damage is responsible for the retrograde amnesia, in addition to diencephalic lesions, Korsakoff's patients sometimes have damage to the cerebellum, brain stem, and neocortex.

Memory Functions of the Hippocampus

One important role of the medial temporal lobes is in declarative memory processing or consolidation. Research on the rat hippocampus suggests, however, that it is involved in memory function for a diverse range of tasks. Before we discuss these tasks, let's look at what is known about the physiology of the hippocampus and the effects of lesions.

The Effects of Hippocampal Lesions in Rats. A role for the hippocampus in memory has been demonstrated by experiments in which rats are trained to get food in a *radial arm maze*, devised by David Olton and his colleagues at Johns Hopkins University. This apparatus consists of arms, or passageways, radiating from a central platform (Figure 23.14a). If a normal rat is put in such a maze, it explores until it finds the food at the end of each arm. With practice, the rat becomes efficient at finding all of the food, going down each arm of the maze just once (Figure 23.14b). To run through the maze without going twice into one of the arms, the rat uses visual or other cues around the

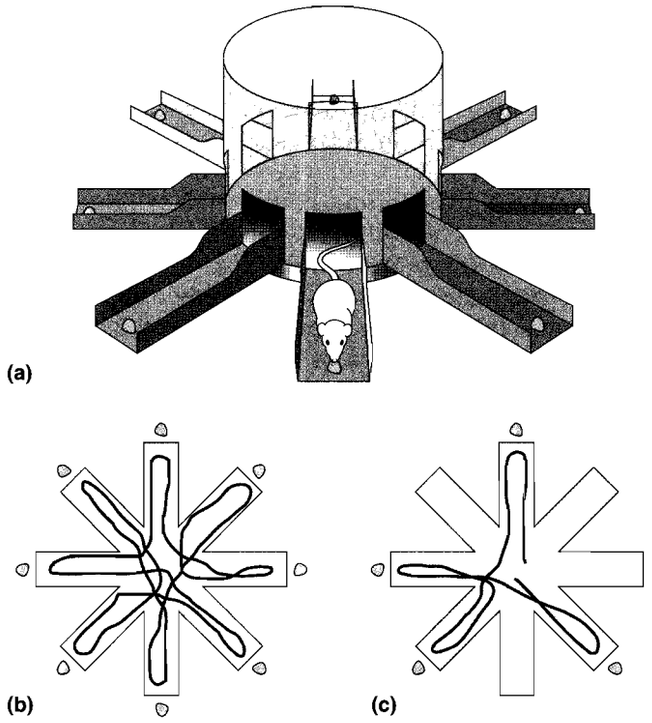

Figure 23.14
Following a rat through a radial arm maze. (a) An eight-arm radial maze. **(b)** The path of a rat through a maze in which all of the arms contain food. **(c)** If a rat learns that four of the eight arms never contain food, it will ignore these and follow a path to only the baited arms. (Source: Parts b and c adapted from Cohen and Eichenbaum, 1993, Fig. 7.4.)

maze to remember where it has already been. The type of memory used to retain information about which arms have been visited was called working memory by Olton. More generally, **working memory** refers to the retention of information needed to guide ongoing behaviors.

If the hippocampus is destroyed before the rat is put in the maze, performance differs from normal in an interesting way. In one sense, rats with lesions seem normal; they learn to go down the arms of the maze and eat the food placed at the end of each arm. But unlike normal rats, they never learn to do this efficiently. Rats with hippocampal lesions go down the same arms more than once, only to find no food after the first trip, and they leave other arms containing food unexplored for an abnormally long time. It appears that the rats can learn the task in the sense that they go down the arms in search of food. But they cannot seem to remember which arms they've already been down.

A variation on the radial arm experiment illustrates an important subtlety in the deficit produced by destroying the hippocampus. Instead of placing food at the end of all of the arms of the maze, food is placed only at the ends of certain arms and never in the other ones. After a bit of practice, a normal rat learns to avoid going down the arms that never contain food (Figure 23.14c). At the same time, the rat learns to get the food in the other arms efficiently, i.e., entering each arm just once. How do rats with hippocampal lesions do on this task? Interestingly, just like normal rats, they are able to learn to avoid the arms that never contain food. But they still are not able to get the food from the other arms without wasting time going down the same arms more than once. Isn't this a little odd? How can we argue that the lesion disrupts the ability to learn the locations of arms that have already been entered, even though the rat can learn to avoid arms that never contain food? Evidently, the key to making sense of these findings is that the information about the no-food arms is always the same each time the rat goes in the maze, whereas the information about which arms the rat has already entered requires working memory and varies from one trial to the next.

Place Cells. In a fascinating series of experiments begun in the early 1970s, John O'Keefe and his colleagues at University College London showed that many neurons in the hippocampus selectively respond when a rat is in a particular location in its environment. Suppose we have a microelectrode implanted in the hippocampus of a rat while it scurries about inside a large box. At first the cell is quiet, but when the rat moves into the northwest corner of the box, the cell starts firing. When it moves out of the corner, the firing stops; when it returns, the cell starts firing again. The cell responds only when the rat is in that one portion of the box (Figure 23.15a). This location, which evokes the greatest response, is called the neuron's *place field*. We try recording from another hippocampal cell, and it too has a place field, but this one fires only when the rat goes to the center of the box. For obvious reasons, these neurons are called **place cells**.

In some ways, place fields are similar to the receptive fields of neurons in the sensory systems. For instance, the location of the place field is related to sensory input such as visual stimuli in the environment. In our experiment with the rat in the box, we could paint images above the four corners, such as a star above the northwest corner, a happy face above the southeast corner, and so on. Consider a cell that responds only when the rat is in the northwest corner of the box near the painted star. Suppose we take the rat out of the box and blindfold it. We then secretly go back and rotate the box 180 degrees so that now the northwest corner has the happy face and the southeast corner has the star. Will the cell we were previously studying respond when the animal is in the northwest corner, or will it respond in the corner where the star

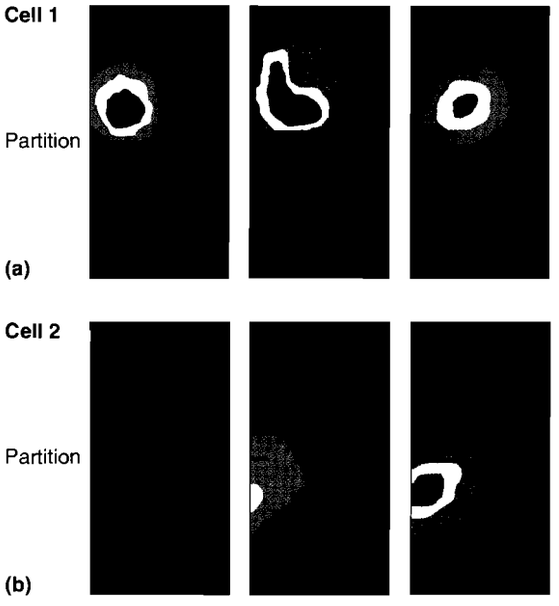

Figure 23.15
Place cells in the hippocampus. A rat explores a small box for 10 minutes (left panels). Then a partition is removed so the rat can explore a larger area (center and right panels). **(a)** Color coding indicates the area in the box where one place cell in the hippocampus responds: red, large response; yellow, moderate response; blue, no response. This cell has a place field in the smaller upper box; when the partition is removed, it stays in the same location. **(b)** In this case, an electrode is next to a cell in the hippocampus that does not respond when the animal is in the smaller upper box (left). In the first 10 minutes after the partition is removed, the cell also does not respond (center). But after another 10 minutes, a place field develops in the new larger box (right). (Source: Adapted from Wilson and McNaughton, 1993, Fig. 2.)

is now located (the southeast corner)? We put the rat back in the box and take off the blindfold. It starts exploring, and the neuron becomes active when the rat goes to the corner near the star. This demonstrates that at least under some conditions, the response is based on visual stimuli.

While place cells are similar to receptive fields in some ways, there are also major differences. For instance, once the animal has become familiar with the box with the images painted in each corner, a neuron continues to fire when the rat goes into the northwest corner even if we turn off the lights so that the animal cannot see the location markers. Evidently, the responses of place cells are related to where the animal *thinks* it is. If there are obvious visual cues, such as the star and happy face, the place fields are based on these cues. But if there are no cues, e.g., because the lights are out, the place cells are still location specific as long as the animal has had enough time to explore the environment and develop a sense of where it is.

Performance in the radial arm maze, discussed earlier, may utilize these place cells, which code for location. Of particular importance in this regard is the finding that the place fields are dynamic. For instance, let's say we first let a rat explore a small box and we determine the place fields of several cells. Then we cut a hole in a side of the box so the animal can explore a larger area. Initially, there are no place fields outside the smaller box. But after the rat has explored its new expanded environment, some cells develop place fields outside the smaller box (Figure 23.15b). These cells seem to *learn* in the sense that they alter their receptive fields to suit the environment. It's easy to imagine how these sorts of cells could be involved in remembering arms already visited in the radial arm maze. And if they are involved in running the maze, it certainly makes sense that performance is degraded by destroying the hippocampus.

Whether there are place cells in the human brain is not known. Positron emission tomography (PET) studies show, however, that the human hippocampus is activated in situations involving virtual or imagined navigation through the environment. In one experiment, subjects were positioned in a PET machine to view a video game on a computer monitor. They could navigate a virtual town in the game by using buttons for forward movement, backward movement, and turning (Figure 23.16a). After the subjects learned their way around the virtual town, their brain activity was recorded while they navigated from an arbitrary starting point to a chosen destination. In a control condition, the person moved through the virtual environment from the same start to finish locations, but there were arrows in the town that always pointed them in the correct direction. In this condition, they did not have to think about how to navigate.

Figure 23.16b shows the difference in brain activity between the navigation condition and the control condition with directional arrows. When the person had to navigate the environment, there was increased activation of the right hippocampus and the left tail of the caudate. The asymmetry in the activation of the left and right hemispheres is an interesting observation that has been repeatedly made, but our primary point is that the hippocampus is particularly active in this spatial navigation task with humans, just as it is in rats. The caudate activation is thought to reflect movement planning. Similar hippocampal activation was observed in an interesting study in which the brains of experienced taxi drivers were imaged as they imagined themselves driving to a destination through the complex streets of London.

Spatial Memory, Working Memory, and Relational Memory. Our discussion of the hippocampus to this point may make it seem that its role is easily defined. First, we saw that performance in a radial arm maze, which requires memory for the locations of arms already explored, is disrupted by hip-

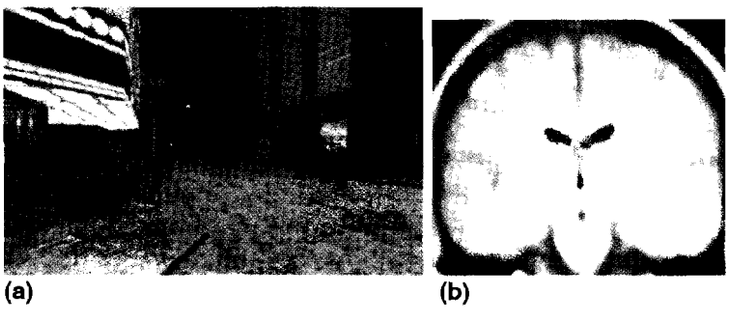

Figure 23.16
Activity in the human brain related to spatial navigation. (a) A virtual town was shown on a computer monitor, and subjects in a PET machine used buttons to navigate the virtual environment. **(b)** In this coronal slice, increased brain activity associated with spatial navigation was observed in the right hippocampus and left tail of the caudate (yellow). (Source: Maguire et al., 1998, Fig. 1.)

pocampal lesions. Second, the responses of neurons in the hippocampus, the place cells, suggests that these neurons are specialized for location memory. This is consistent with O'Keefe's hypothesis that the hippocampus is specialized for creating a spatial map of the environment. In one sense it is undeniable that the hippocampus, at least in rats, plays an important role in spatial memory. Others argue, however, that this is not the best description of what the hippocampus does. In Olton's original studies using the radial arm maze, he described the result of hippocampal lesions as a deficit in working memory. The rats were not able to retain recently acquired information concerning arms already explored. Thus, working memory may be one aspect of hippocampal function. This would explain why the rats with lesions could avoid going down arms that never contained food but still not remember which arms they had recently visited. Presumably after training, the information about no-food arms was saved in long-term memory, but working memory was still required to avoid the arms where food had already been retrieved.

A more recent hypothesis attempting to integrate a range of experimental findings has been put forward by behavioral neuroscientists Neal Cohen at the University of Illinois, Howard Eichenbaum at Boston University, and their colleagues. Cohen and Eichenbaum describe the function of the hippocampus, in conjunction with other structures of the medial temporal lobe, as involving relational memory. The basic idea of **relational memory** is that highly processed sensory information comes into the hippocampus and nearby cortex, and processing occurs, leading to the storage of memories in a manner that ties together or relates all of the things happening at the time the memory was stored. For example, as you read this book, you may form memories relating multiple things: specific facts, illustrations that catch your eye, interesting passages, the arrangement of material on the page, and information about the sounds or events going on around you as you read. You may have had the experience of searching for a particular passage in a book by searching for a page that looks a certain way that you remember. It is also a common event that remembering one thing (such as the theme song to an old television show) brings back a flood of related facts (the characters in the show, your living room at home, the friends you watched with, and so on). Interconnectedness is a key feature of declarative memory storage.

To navigate its environment, a rat could use either a mental map of space or relational memories associated with environmental cues. The distinction between the spatial map and relational memory hypotheses is illustrated in Figure 23.17. If there is a spatial map, one would expect place fields to be ordered in the hippocampus as the locations are in space, much like the retinotopic receptive fields in visual cortex. Experts disagree about the extent to which hippocampal place cells provide such an organized map of the entire area around the animal. In a relational memory scheme, neurons encode information about place as a series of simple associations between nearby ob-

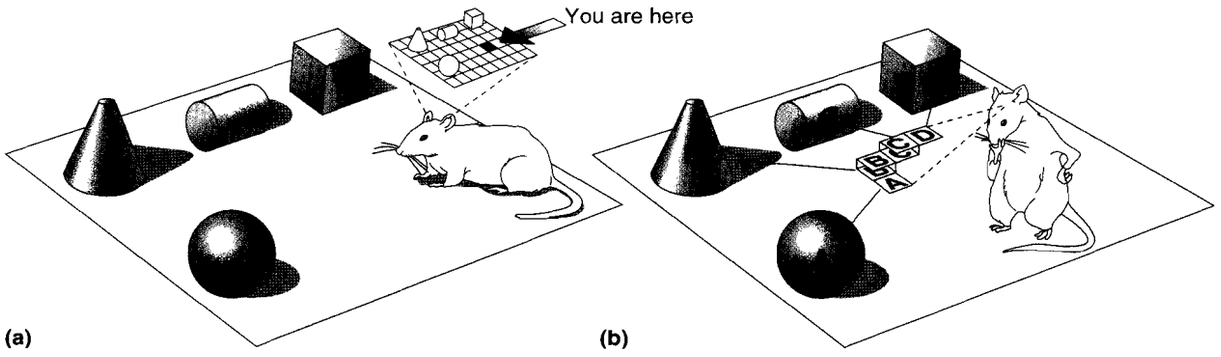

Figure 23.17
Spatial navigation based on (a) a spatial map and (b) a series of relational memories.
(Source: Adapted from Eichenbaum et al., 1999.)

jects and concurrent sounds and smells. For example, in Figure 23.17b, "ball A is below cone B" would be one memory, and "cone B is to the left of cylinder C" would be another. Strung together, such relational memories could provide an understanding of the layout of the environment without having a complete, organized map in the hippocampus.

Whether or not relational memory is the principal function of the hippocampus has not been settled. It is a useful concept, however. In the maze experiments, a case can be made that the rat performs the task by storing memories of the arms it has been down in terms of the sensory cues in the room and the time a given arm was entered. Evidence also suggests that place cells may encode relational information of types other than spatial location. A simple example is that the responses of neurons with place fields are sometimes also affected by other factors, such as the speed or direction the rat is moving.

The responses of hippocampal neurons are also sometimes determined by nonspatial factors. This was demonstrated in an experiment in which Eichenbaum, Cohen, and their colleagues trained rats to discriminate odors. At one end of the rat's cage were two ports putting out two odors for the animal to sniff (Figure 23.18). For each pair of odors, the animal was trained to go toward the port releasing one odor and avoid the other port. The researchers found that some neurons in the hippocampus became selectively responsive for certain pairs of odors. Moreover, the neurons were particular about which odor was at which port—they would respond strongly with odor 1 at port A and odor 2 at port B, but not with the odors switched to the opposite ports. This indicates that the response of the hippocampal neurons relates the specific odors, their spatial locations, and the fact that they are pre-

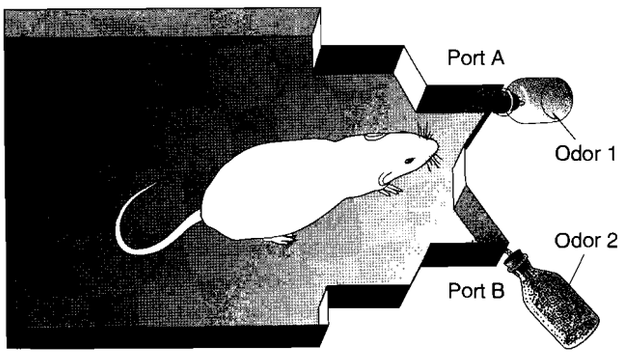

Figure 23.18
An odor discrimination experiment used to study relational memory. For various combinations of odors, rats were trained to move toward a port emitting one odor and avoid the other port. (Source: Adapted from Eichenbaum et al., 1988, Fig. 1.)

sented separately or together. It was also shown that hippocampal lesions produce deficits on this discrimination task.

THE STRIATUM AND PROCEDURAL MEMORY

Thus far, we have focused on the brain systems involved in the formation and retention of declarative memories, partly because declarative information is what we commonly mean when we say we remember something. In addition, the neural basis of nondeclarative memory is complex because different types seem to involve different brain structures. As indicated in Figure 23.1, various kinds of nondeclarative memory are thought to involve different parts of the brain. As an example of nondeclarative memory, we will take a look at evidence supporting the involvement of the striatum in habit learning and procedural memory.

Recall from Chapter 14 that the basal ganglia are important for the control of voluntary movements. Two elements of the basal ganglia are the caudate nucleus and the putamen, and together they form the **striatum**. The striatum sits at a key location in the motor loop, receiving input from frontal and parietal cortex and sending output to thalamic nuclei and cortical areas involved in movement. Several lines of evidence in studies of rodents and humans suggest that the striatum is critical for the procedural memory involved in forming behavioral habits.

Rodent Recordings and Lesions in the Striatum

The amnesia experienced by H. M. is surprising, in part, because he is able to learn new habits despite his complete inability to form new declarative memories. Indeed, this is one of the most compelling reasons for hypothesizing that procedural memory uses distinct circuitry. In the monkey model of amnesia, we saw that the formation of new declarative memories could be disrupted by making small lesions in the rhinal cortex of the medial temporal lobe. Such a lesion has relatively little effect on procedural memory, which raises an obvious question: Are there comparable lesions that disrupt procedural memory without affecting declarative memory? In rodents, lesions to the striatum have this effect.

In one study, rats had to learn two versions of the radial arm maze task. The first was the standard version in which the rat must move as efficiently as possible to retrieve the food from each of the baited arms of the maze. In the second version, small lights were illuminated above one or more arms containing food, and the unlit arms had no food. The lights could be turned on or off at any time. In this case, optimal performance meant that the animal kept returning to retrieve food from lit arms as long as they were lit and avoided arms that were never lit. The standard maze task was designed to require the use of declarative memory. The "light" version of the task was intended to draw on procedural memory because of the consistent association between the presence of food and illuminated lights. The rat does not have to remember which arms it has already explored; it must simply form a habit based on the association that light correlates with food. The rat's performance on the light task is analogous to the habits H. M. was able to form, such as mirror drawing.

Performance on the two versions of the radial arm maze task was affected in markedly different ways by two types of brain lesions. If the hippocampal system was damaged (in this case, by a lesion in the fornix that sends hippocampal output), performance was degraded on the standard maze task but was relatively unaffected on the light version. Conversely, a lesion in the striatum impaired performance of the light task but had little effect on the

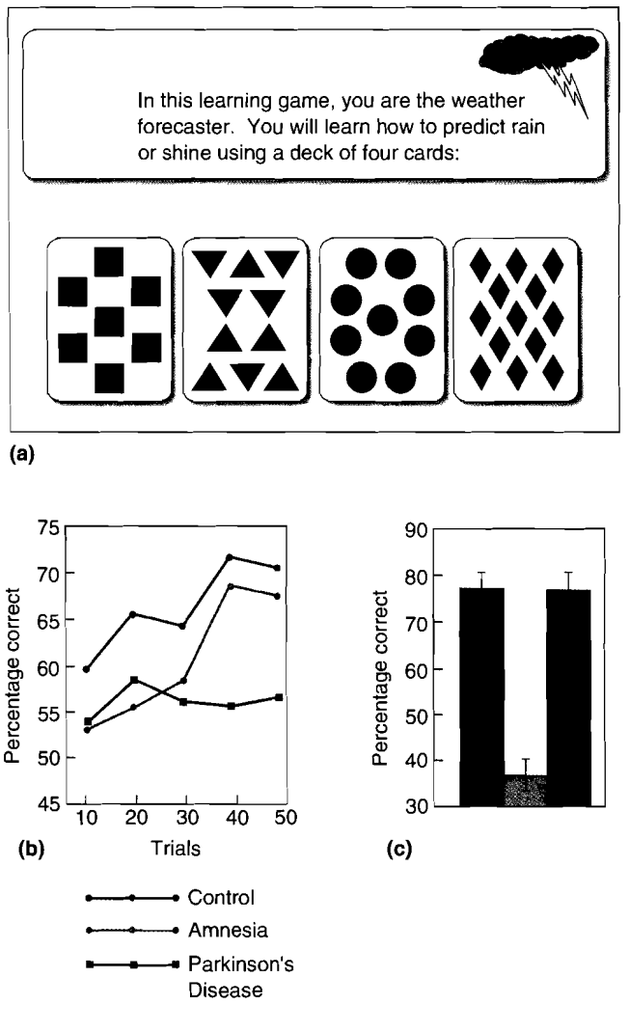

Figure 23.20
The performance of patients with amnesia and Parkinson's disease on two memory tasks. (a) Four cue cards were presented in various combinations associated with the icons indicating sun or rain. Based on repeated exposure to the combinations, patients had to learn to predict sun or rain by inferring the associations. **(b)** With successive trials, control subjects and amnesic patients improved on the association task. Parkinson's patients showed little improvement. **(c)** On a test of declarative memory formation (a questionnaire), Parkinson's patients performed similarly to control subjects, and amnesia patients were greatly impaired. (Source: Adapted from Knowlton et al., 1996.)

The Prefrontal Cortex and Working Memory

One of the most obvious anatomical differences between primates (especially humans) and other mammals is that primates have a large frontal lobe. The rostral end of the frontal lobe, the **prefrontal cortex**, is particularly highly developed (Figure 23.21). Compared with the functions of sensory and motor cortical areas, the function of prefrontal cortex is relatively poorly understood. But because it is so well developed in humans, it is often assumed that prefrontal cortex is responsible for those characteristics, such as self-awareness and the capacity for complex planning and problem solving, that distinguish us from other animals. One reason for thinking that prefrontal cortex may be involved in learning and memory is that it is interconnected with the medial temporal lobe and diencephalic structures previously discussed (Figure 23.22).

Some of the first evidence suggesting that the frontal lobe is important for learning and memory came from experiments performed in the 1930s using a *delayed-response task*. In this task, a monkey first sees food being placed in a well below one of two identical covers in a table. A delay period follows, during which the animal cannot see the table. Finally, the animal is allowed to see the table again and receives the food as a reward if it chooses the correct well. Large prefrontal lesions seriously degrade performance on this delayed-response task and other tasks including a delay period. Moreover, the

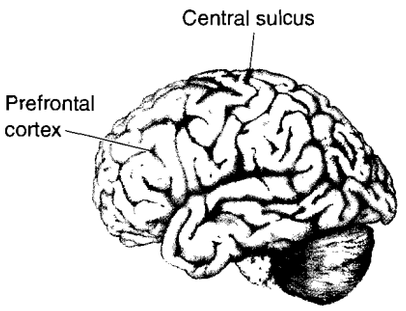

Figure 23.21
Prefrontal cortex. The prefrontal cortex at the rostral end of the frontal lobe receives afferents from the medial dorsal nucleus of the thalamus.

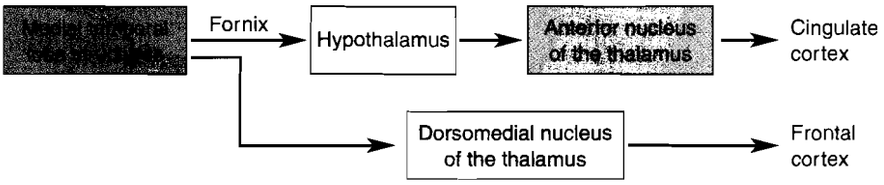

Figure 23.22
Connections between cortical association areas and the medial temporal lobe. Prefrontal cortex and cingulate cortex receive afferents from structures of the medial temporal lobe.

monkeys perform increasingly poorly as the delay period is lengthened. These results imply that prefrontal cortex plays some important role in memory.

Experiments conducted more recently suggest that prefrontal cortex is involved with working memory for problem solving and the planning of behavior. One piece of evidence comes from the behavior of humans with lesions in prefrontal cortex. These people usually perform better on simple memory tasks, such as recalling information after a delay period, than do those with medial temporal lesions. In more complex tasks, however, humans with prefrontal damage show marked deficits. Recall the case of Phineas Gage, discussed in Chapter 18. Having sustained severe frontal lobe damage (an iron bar passing through the head qualifies as severe), Gage had a difficult time maintaining a course of behavior after his injury. Although he could carry out behaviors appropriate for various situations, he had difficulty planning and organizing these behaviors, perhaps because of the damage to his frontal lobe.

A task that brings out the problems associated with prefrontal cortical damage is the Wisconsin card-sorting test. A person is asked to sort a deck of cards having a variable number of colored geometric shapes on them (Figure 23.23). The cards can be sorted by color, shape, or number of symbols, but at the beginning of the test, the subject isn't told which category to use. By putting cards into stacks and being informed when errors occur, however, the subject learns what the current sorting category is. After ten correct card placements are made, the sorting category is changed, and the routine starts over again. To perform well on this test, the person must use memory of previous cards and errors made to plan the next card placement. People with

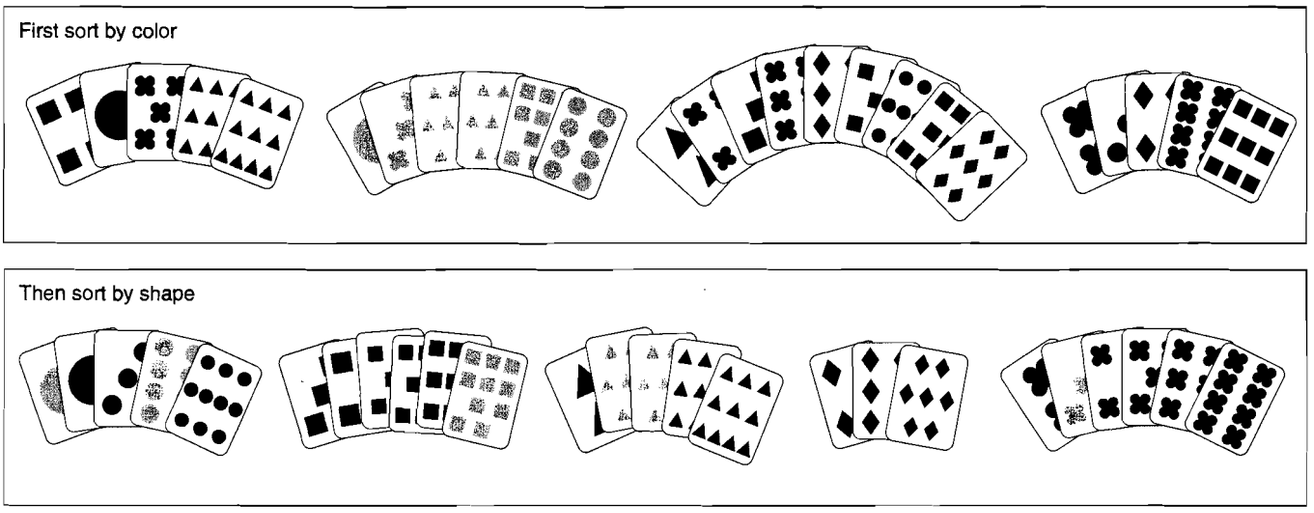

Figure 23.23
The Wisconsin card-sorting test. Cards containing various numbers of colored symbols must first be sorted by color. After a string of correct responses is made, the sorting category is changed to shape.

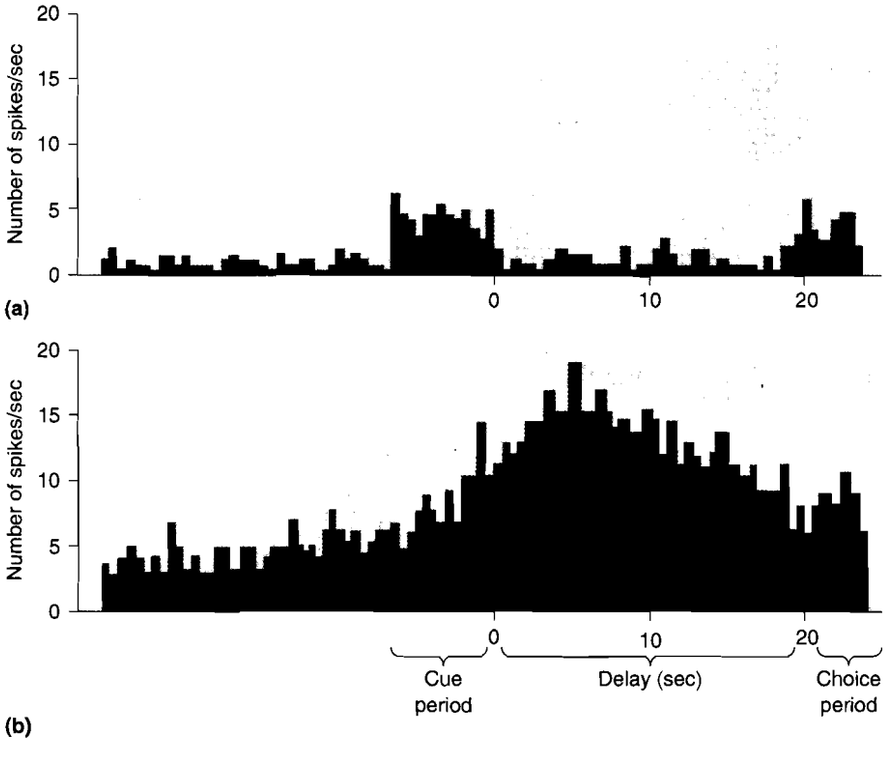

Figure 23.24
Neural responses in monkey prefrontal cortex. The two histograms show the activity of cells in prefrontal cortex recorded while the animal performed a delayed-response task. During a cue period of 7 seconds, within the view of the monkey food is placed in one of two wells. During the delay period, the animal cannot see the food wells; after the delay, it is allowed to choose a well to receive a food reward (the choice period). **(a)** This cell responds when the well is first baited with food and again when the animal exposes the well to get the food. **(b)** This cell responds most strongly during the delay period, when there is no visual stimulus. (Source: Adapted from Fuster, 1973, Fig. 2.)

prefrontal lesions have great difficulty on this task when the sorting category is changed; they continue to sort according to a rule that no longer applies. It appears that they have difficulty using recent information (i.e., data in working memory) to change their behavior.

The same sort of deficit is seen in other tasks. For example, a person with a prefrontal lesion may be asked to trace a path through a maze drawn on a piece of paper. While the patient understands the task, he or she repeatedly makes the same mistakes, returning to blind alleys. In other words, these patients do not learn from their recent experience in the same way that a normal person does. And when they make mistakes, they may have difficulty returning to an earlier point in the maze and instead start over from the beginning.

The neurons in prefrontal cortex have a variety of response types, some of which may reflect a role in working memory. Figure 23.24 shows two response patterns obtained while a monkey performed a delayed-response task. The neuron in the top trace responded while the animal saw the location of the food, was unresponsive during the delay interval, and responded again when the animal made a choice (Figure 23.24a). The response of the neuron simply correlates with the presentation of the stimuli. Perhaps more interesting is the response pattern of the other neuron, which increased its firing rate only during the delay interval (Figure 23.24b). This cell was not directly activated by the stimuli in the first or second interval in which it saw the food wells. The increased activity during the delay period may be related to the retention of information needed to make the correct choice after the delay (i.e., working memory).

Lateral Intraparietal Cortex (Area LIP) and Working Memory

In recent years, several other cortical areas have been found to contain neurons that appear to retain working memory information. In Chapter 14, we

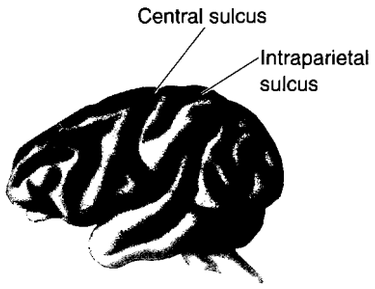

Figure 23.25
LIP buried in the intraparietal sulcus. Working memory responses are observed in some neurons in this area involved in visually guided behaviors.

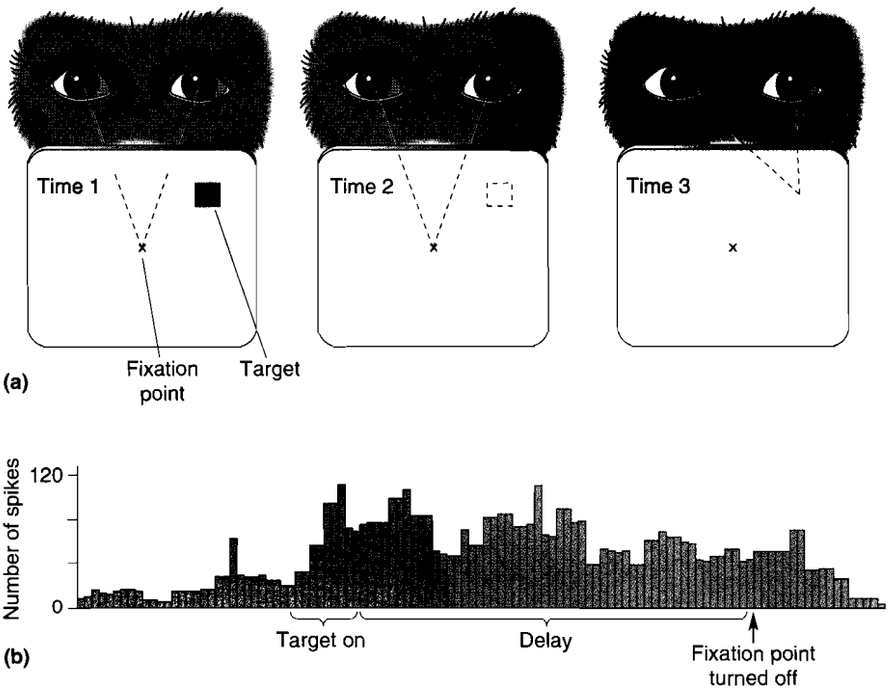

Figure 23.26
The delayed-saccade task. (a) After fixating on a central point, a target goes on and off at a peripheral location. There is a delay period after the target goes off in which the monkey must continue to fixate on the central point. At the end of the delay period, the fixation point goes off, and the animal knows to move its eyes to the remembered location of the target. **(b)** The histogram shows the response of an LIP neuron. The neuron begins firing when the target is presented and continues firing until after the fixation point is gone and the saccadic eye movement begins. (Source: Adapted from Goldman-Rakic, 1992, Fig. p. 113, and Gnadt and Andersen, 1988, Fig. 2.)

saw an example in area 6 (see Figure 14.9). Another example is provided by **lateral intraparietal cortex (area LIP)**, buried in the intraparietal sulcus (Figure 23.25). Because electrical stimulation here elicits saccades, area LIP is thought to be involved in guiding eye movements. The responses of many neurons suggest that they are involved in a type of working memory. This pattern is evident in a *delayed-saccade task* in which the animal fixates on a spot on a computer screen and a target is briefly flashed at a peripheral location (Figure 23.26a). After the target disappears, there is a variable delay period. At the end of the delay period, the fixation spot goes off, and the animal's eyes make a saccadic movement to the remembered location of the target. The response of an LIP neuron while a monkey performs this task is shown in Figure 23.26b. The neuron begins firing shortly after the peripheral target is presented; this seems like a normal stimulus-evoked response. But the cell keeps firing throughout the delay period in which there is no stimulus, until saccadic movements finally occur. Further experiments using this delayed-saccade task suggest that the response of the LIP neuron is temporarily holding information that will be used to produce the saccades.

Other areas in parietal and temporal cortex have been shown to have analogous working memory responses. These areas seem to be modality specific, just as the responses in area LIP are specific to vision. This is consistent with the clinical observation that there are distinct auditory and visual working memory deficits in humans produced by cortical lesions.

CONCLUDING REMARKS

A clear message from the topics discussed in this chapter is that learning and memory are not confined to a single place in the brain. It is not the case that a small number of specialized "memory cells" store our life experiences and learned behaviors independent from the rest of brain function. This is logical, considering that behavioral adaptability is critical for survival and that the required brain adaptations involve sensory systems (you recognize what you see over there as an angry dog that might bite you), motor control systems (the combination of muscle contractions required to keep you atop a unicycle), and systems more specialized for storing facts. In our effort to understand the learning process itself, we are still at an early stage. Declarative memory depends heavily on the hippocampus and related structures, procedural memory involves the striatum, and working memory traces are found in many brain locations.

But how do different parts of the brain interact so that we learn? We've said that engrams may exist in temporal lobe neocortex, among other places. But what is the physiological basis for the memory storage? When we try to remember a phone number, an interruption can make us forget, suggesting that memories are initially held in a particularly fragile form. Long-term memory is much more robust, however; it can survive interruption, anesthesia, and life's normal bumps and traumas. Partly because of this robustness, it is thought that memories are ultimately stored in structural changes in neocortex. Our brain is constantly undergoing rewiring, to a certain degree, to adapt to life's experiences. The nature of these structural changes in the brain, which underlie learning and memory, are the subject of Chapter 24.

KEY TERMS

Types of Memory and Amnesia
learning (p. 740)
memory (p. 740)
declarative memory (p. 740)
nondeclarative memory (p. 740)
procedural memory (p. 740)
long-term memory (p. 741)
short-term memory (p. 741)
memory consolidation (p. 743)
amnesia (p. 743)
retrograde amnesia (p. 743)
anterograde amnesia (p. 744)

The Search for the Engram
engram (p. 745)
cell assembly (p. 747)

The Temporal Lobes and Declarative Memory
hippocampus (p. 754)
entorhinal cortex (p. 754)
perirhinal cortex (p. 754)
parahippocampal cortex (p. 754)
fornix (p. 756)
delayed non-match to sample (DNMS) (p. 757)
recognition memory (p. 758)
Korsakoff's syndrome (p. 760)
working memory (p. 761)
place cell (p. 762)
relational memory (p. 764)

The Striatum and Procedural Memory
striatum (p. 766)

The Neocortex and Working Memory
prefrontal cortex (p. 769)
lateral intraparietal cortex (area LIP) (p. 772)

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Chapter 23

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