CHAPTER

13

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Donna was born on June 14, 1933. Her memory of the period from 1933 to 1937 is sketchy, but those who knew her as a baby report that she was like most other infants. At first, she could not talk, walk, or use a toilet. Indeed, she did not even seem to recognize her father, although her mother seemed more familiar to her. Like all children, Donna grew quickly, and in no time she was using and understanding simple language and could recognize many people by sight almost instantly. Donna began taking dancing lessons when she was four and was a "natural." By the time she finished high school she had the training and skill necessary for a career as a dancer with a major dance company. She remembers vividly the day that she was chosen to play a leading role in *The Nutcracker*. She had marveled at the costumes as she watched the popular Christmas ballet as a child, and now she was to be dancing in those costumes!

Donna's part in *The Nutcracker* had an even greater impact on her life when she met a man at a party after the last performance. He had seen her dance and took the opportunity to tell her how much he had enjoyed it. He was a young assistant professor of paleontology who studied dinosaur eggs in Montana. She was swept off her feet, and they married in 1958. Although her career as a dancer was soon interrupted by the births of two children, Donna never lost interest in dancing. In 1968, once both her children were in school, she began dancing again with a local company. To her amazement, she still could perform most of the movements, although she was rusty on the classic dances that she had once memorized so meticulously. Nonetheless, she quickly relearned. In retrospect, she should not have been so surprised, as she had always had an excellent memory.

One evening in 1990, while on a bicycle ride, Donna was struck by a drunk driver. Although she was wearing a helmet, she suffered a closed head injury that put her in a coma for several weeks. As she regained consciousness, she was confused and had difficulty in talking and in understanding others. Her memory was very poor; she had spatial disorientation and often got lost; she had various motor disturbances; and she had difficulty recognizing anyone but her family and closest friends.

Over the ensuing 10 months, Donna regained most of her motor abilities and language skills, and her spatial abilities improved significantly. Nonetheless, she was short-tempered and easily frustrated by the slowness of her recovery, symptoms that are typical of people with closed head injuries. She suffered periods of depression. She also found herself prone to inexplicable surges of panic when doing simple things. On one occasion early in her rehabilitation, she was shopping in a large supermarket and became overwhelmed by the number of salad dressing choices. She ran from the store, and it was only after she sat outside and calmed herself that she could go back inside to continue shopping.

Two years later, Donna was dancing once again, but she now found it very difficult to learn new steps. Her emotions were still unstable, which was a strain on her family, but her episodes of frustration and temper outbursts became much less frequent. A year later, they were gone and her life was not obviously different from that of other 57-year-old women. She did have some cognitive changes that persisted, however. She seemed unable to remember the names or faces of new people she met and was unable to concentrate if there were distractions such as a television or radio playing in the background. She could not dance as she had before her injury, although she did work at it diligently. Her balance on sudden turns gave her the most difficulty; rather than risk falling, she retired from her life's first love.

Donna's experiences demonstrate one of the most intriguing and important properties of the human brain: its capacity for continuously changing its structure, and ultimately its function, throughout a lifetime. This capacity to change, which is known as **brain plasticity,** allows the brain to respond to changes in the environment or within the organism. In describing the events of Donna's life, we can see several types of behavioral change that must be correlated with different plastic changes in the brain. First, during her early childhood, Donna's brain changed dramatically in structure as she learned about the world and how to respond to it. She had to learn to use language, to distinguish different faces, to walk, to ride a bicycle, to read, to dance, and so on. Because her brain is solely

responsible for her behavior, her brain somehow changed to reflect her experiences and new abilities. When Donna reached puberty, her body changed and so did her thoughts. Her dreams often had sexual content; because dreams are a product of the brain, there must have been some change in her brain activity for her dreams to change so dramatically. When Donna returned to dancing after a 10-year break, she found that she had retained much of her skill, even though she had not practiced at all. In this case the brain saved the earlier changes. After her accident, Donna had to "relearn" how to talk, to walk, and so on. In actual fact, she did not go through the same process of learning that she had experienced as a baby, but something in her brain had to change in order to allow her to regain her lost abilities. That change must have had some limits, however, because she never did recover her memory or her ability to learn new dances.

One lesson of the story of Donna is that although we tend to look at the brain as a relatively static structure that controls our behavior, the brain changes throughout our lifetime, and it is these changes that allow us to modify our behavior. If we reflect upon our own lives, we can easily compile a list of the experiences that must change our brains. A typical list would include the profound changes in brain and behavior during development that we discussed in Chapter 7, as well as the acquisition of culture, preferences for certain foods or beverages or art or other experiences, the ability to cope with the progressive loss of brain cells during the aging process, and, for many people (including Donna), the capacity to accommodate to neurological injury or disease. One common characteristic of all these examples is that they include what we would typically describe as some form of learning. Understanding how the brain supports learning is one of the fundamental questions of neuroscience.

The analysis of learning and the brain can be approached on several levels:

1. We can ask questions about the nature of learning. For example, is all learning the same, or are there different types of learning?
2. If there are different types of learning, then we might expect that there would be separate brain circuits related to the different types. In Chapter 5, we noted that synapses change with events such as those observed in long-term enhancement, but such changes could occur anywhere in the brain. The bigger question is just where such changes might occur when we learn specific types of information.
3. We can investigate the nature of the neural changes that support learning. One way to do this is to describe the changes in neurons when they are exposed to specific sensory experiences. Another is to look at the neural changes that accompany various forms of brain plasticity, such as recovery from brain injury or addiction to drugs.

These three approaches to the study of learning are presented in this chapter. The overriding goal, however, is to generalize beyond learning in order to understand the nature of behavior and the changing brain.

WHAT ARE LEARNING AND MEMORY?

Learning is a relatively permanent change in an organism's behavior as a result of experience. **Memory** refers to the ability to recall or recognize previous experience. Memory thus implies a mental representation of the previous experience. This mental representation is sometimes referred to as a *memory trace*, and it is presumed that a memory trace reflects some type of change in the brain. Note that what we know about the process of learning and the formation of memories is inferred from changes in behavior, not observed directly. The study of learning and memory therefore requires the creation of behavioral measures to evaluate such behavioral changes. We begin our discussion of the nature of learning by looking at the ways in which animals are studied in the laboratory. We then look at what general types of learning can be identified from such studies.

Brain plasticity. The ability of the brain to change its structure in response to experience, drugs, hormones, or injury.

Learning. A relatively permanent change in an organism's behavior as a result of experience.

Memory. The ability to recall or recognize previous experience.

Studying Memory in the Laboratory

One of the challenges for psychologists studying memory in laboratory animals (or people) is to get the subjects to reveal what they can remember. Because laboratory animals do not talk, investigators must devise ways for a subject to show its knowledge. Different species can "talk" to us in different ways, so the choice of test must be matched to the capabilities of the species. In the study of rodents,mazes or swimming pools are typically used because rodents live in tunnels and around water. Studies of monkeys have taken advantage of the monkeys' sharp vision and avid curiosity by requiring them to look under objects for food or at television monitors. When birds are the subjects, it is common to use natural behaviors such as singing. And for human subjects there is a tendency to use paper-and-pencil tests. The result is that psychologists have devised hundreds of different tests in the past century and,in doing so, have shown that there are many types of learning and memory, each of which appears to have its own neural circuitry. Let us consider some examples of how animals can be trained to "talk."

PAVLOVIAN CONDITIONING

At the beginning of the twentieth century, two very different traditions of studying learning and memory emerged. The Russian physiologist Ivan Pavlov discovered that when a food reward accompanied some stimulus, such as a tone, dogs learned to associate the stimulus with the food. Then, whenever they heard the tone, they would salivate even though no food was present. This type of learning has many names, including **Pavlovian conditioning,** *respondent conditioning,* and *classical conditioning*, and its characteristics have been documented by many studies.A key feature of Pavlovian conditioning is that animals learn the association between two stimuli (such as the presentation of the food and the tone) and tell us they have learned it by giving the same response (such as salivation) to both stimuli. Pet owners are familiar with this type of learning: to a cat or dog, the sound of a can opener is a clear stimulus for food. Experimentally, two forms of Pavlovian conditioning are commonly used today: eye-blink conditioning and fear conditioning. These have proved especially useful because they are associated with neural circuits in discrete brain regions.

Pavlovian conditioning. A learning procedure whereby a neutral stimulus (such as a tone) comes to elicit a response because of its repeated pairing with some event (such as the delivery of food); also called classical conditioning or respondent conditioning.

Eye-blink conditioning has been used to study Pavlovian learning in rabbits and people (Figure 13-1). In these studies, a tone (or some other stimulus) is associated with a painless puff of air to the eye of the subject. The tone, which is known as the **conditioned stimulus** (CS), comes to elicit a blink that is initially produced by the air puff, which is known as the **unconditioned response** (UCR), because it is the normal reaction to a puff of air. Thus, the subject tells us that it has learned that the signal stimulus predicts the puff by blinking in response to the signal alone—a **conditioned response** (CR). This form of learning is mediated by circuits in the cerebellum. The cerebellum does not have special circuits just for eye-blink conditioning, which is an artificial situation. Rather, the cerebellum has circuits designed to pair various motor responses with environmental events. The eye-blink conditioning experiments simply take advantage of this predisposition.

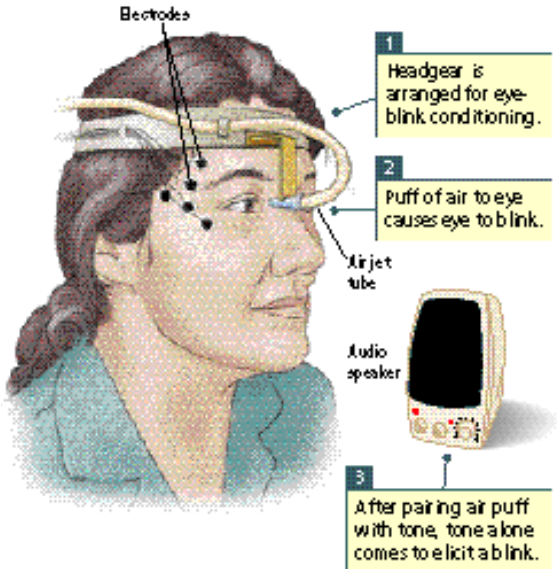

Figure 13-1

A subject wearing headgear arranged for eye-blink conditioning. The apparatus delivers a puff of air to the eye, which causes the subject to blink. When the air puff is paired with a tone, the subject learns the association and subsequently blinks to the tone alone. This form of learning is mediated by circuits in the cerebellum.

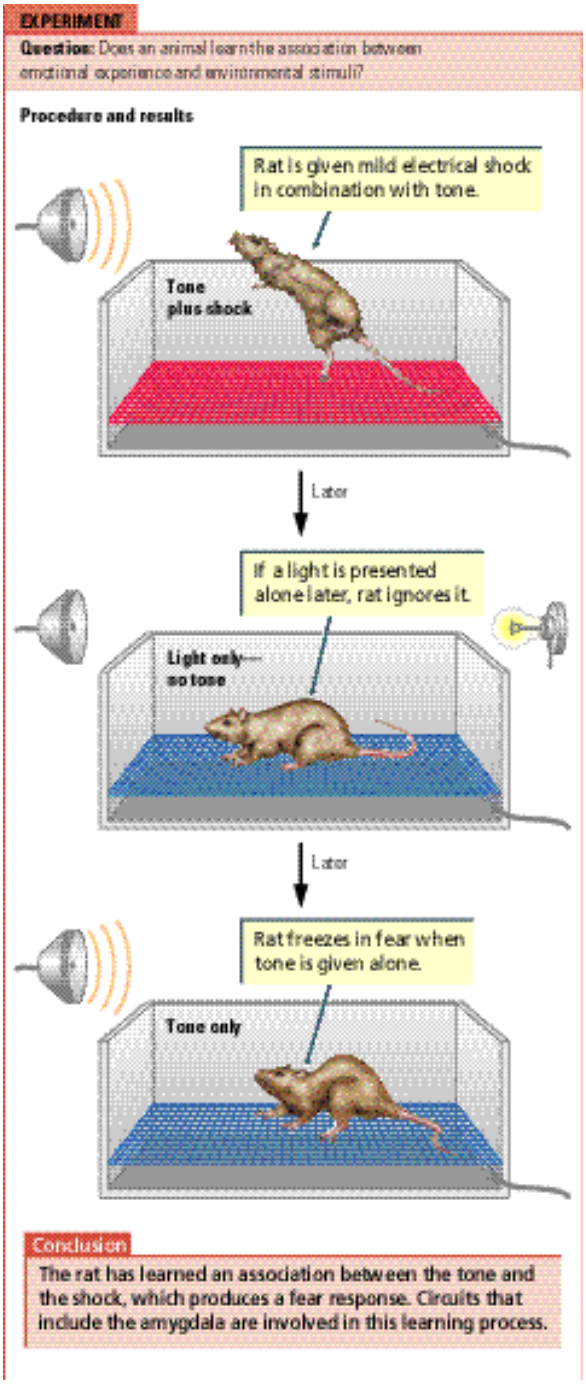

Figure 13-2

An example of a conditioned emotional response. A rat is given a mild electric shock in combination with a tone (*top*). If a light is presented alone later, the animal ignores it (*center*). When the tone is presented alone later, the rat freezes in fear because it has learned an association between the tone and a shock (*bottom*). The amygdala and associated circuits play a key role in this form of conditioning.

In **fear conditioning,** a noxious stimulus is used to elicit fear. A rat or other animal is placed in a box that has a grid floor through which a mild but noxious electric current can be passed. As shown in Figure 13-2, a tone (the CS) is presented just before a brief, unexpected, mild electric shock. (This shock is roughly equivalent to the static-electrical shock we get when we rub our feet on a carpet and then touch a metal object or another person.) When the tone is later presented without the shock, the animal will act as though afraid. For example, it may become motionless and may urinate in anticipation of the shock. Presentation of a novel stimulus, such as a light, in the same environment has little effect on the animal. Thus, the animal tells us that it has learned the association between the tone and the shock. Circuits of the amygdala, rather than the cerebellum, mediate fear conditioning. Although both eye-blink and fear conditioning are Pavlovian, different parts of the brain mediate the learning.

INSTRUMENTAL CONDITIONING

The second tradition of studying learning and memory was begun in the United States by Edward Thorndike (1898). Thorndike was interested in how animals solved problems. In one famous series of experiments, Thorndike placed cats in a box with a plate of fish outside it (Figure 13-3). The only way for a hungry cat to get to the fish was to figure out how to get out of the box. The solution was to press on a lever, which activated a system of pulleys that opened the box's door. The cat gradually learned that its actions had consequences: on the initial trial, the cat would touch the releasing mechanism only by chance as it restlessly paced inside the box. The cat apparently learned that something it did opened the door, and it would tend to repeat the behaviors that had occurred just prior to the door opening. After a few trials, the cat would take just seconds to get the door open so it could devour the fish.

Later studies by B. F. Skinner (e.g., 1938) used a similar strategy to train rats to press bars or pigeons to peck keys to obtain food. Many animals will learn to bar press or key peck if they are simply placed into the apparatus and allowed to discover the response necessary to obtain the reward, just as Thorndike's cats learned to escape the boxes. This type of learning is referred to as **instrumental conditioning** or *operant conditioning*. The subject indicates that it has learned the association between its actions and the consequences by increasing the speed at which it can perform the task. The variety of such instrumental associations is staggering, as we are constantly learning the association between our behavior and its consequences. It should be no surprise, therefore, that instrumental learning is

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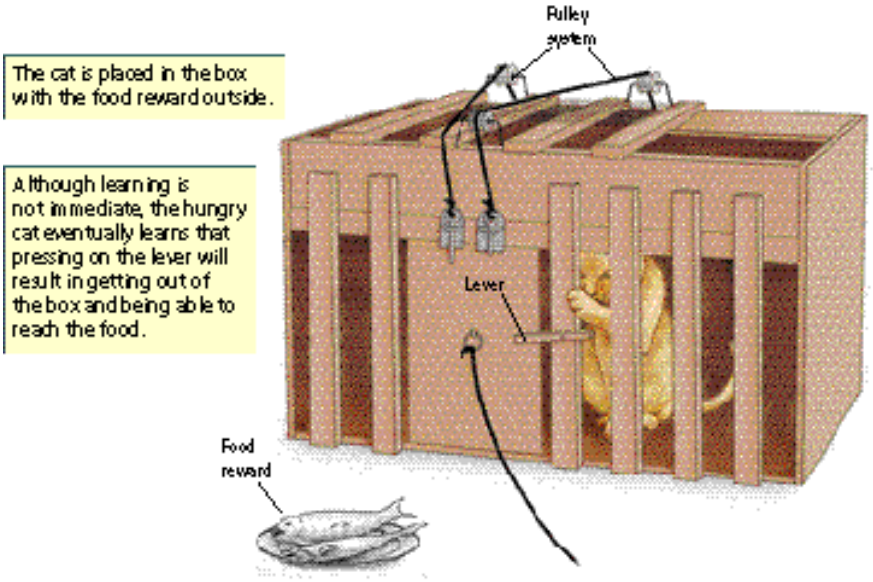


Figure 13-3

An example of the puzzle box used by Thorndike to study learning in cats. The task is for the cat to open the door to get to the fish reward.

not localized to any particular circuit in the brain. The circuits needed vary with the actual requirements of the task, as is demonstrated by the following examples.

Richard Morris devised a task in 1980 that has become popular in research in learning and memory. He placed rats in a large swimming pool in which there was an escape platform that was invisible to the rats because it was just under the water's surface.(Figure 13-4A shows the setup.) The task for the rat was to discover that there was an escape and then to figure out where the platform was. In one version of the test, which is illustrated in Figure 13-4B, the only available cues were distal ones—that is, external to the pool. Because no single cue would identify the location of the platform, the rats had to learn the relationship between several cues in the room and the platform's location. This obviously requires **visuospatial learning,** or the use of visual information to identify an object's spatial location. Rats normally learn the Morris task in just a few trials such that when placed anywhere in the pool, they can swim directly to the hidden platform. We can infer that a rat that is able to swim but is unable to learn this task has some disturbance in the neural circuits underlying visuospatial learning,

In a variation of the task, once rats are trained to find the platform, the location of the platform is changed (Figure 13-4C).The platform is moved to a new position every day; the rats must find the platform on the first trial in the pool and then go to that location for the remainder of that day's trials. In this case, the rats' task is to learn not only the platform's location with respect to the visual world but also its new location each day. Rats quickly learn this puzzle and form what is known as a learning set. A **learning set** is an understanding of how a problem can be solved through the use of a rule that can be applied in many different situations. In the current example,the rule is that the successful solution (finding the platform) requires a shift in strategy when the old strategy fails. Well-trained animals need only a single trial to learn the platform's location each day and will swim flawlessly to that location on subsequent trials. This type of task, in which the rat must keep track of a specific piece of information on a given day, places demands on the brain that are clearly different from the simpler Morris version, in which the learning is gradual, much like that in Thorndike's cats.

Fear conditioning. The learning of an association between a neutral stimulus and and a noxious event such as a shock.

Instrumental conditioning. A learning procedure in which the consequences (such as obtaining a reward) of a particular behavior (such as pressing a bar) increase or decrease the probability of the behavior occurring again; also called operant conditioning.

Learning set. An understanding of how a problem can be solved with a rule that can be applied in many different situations.

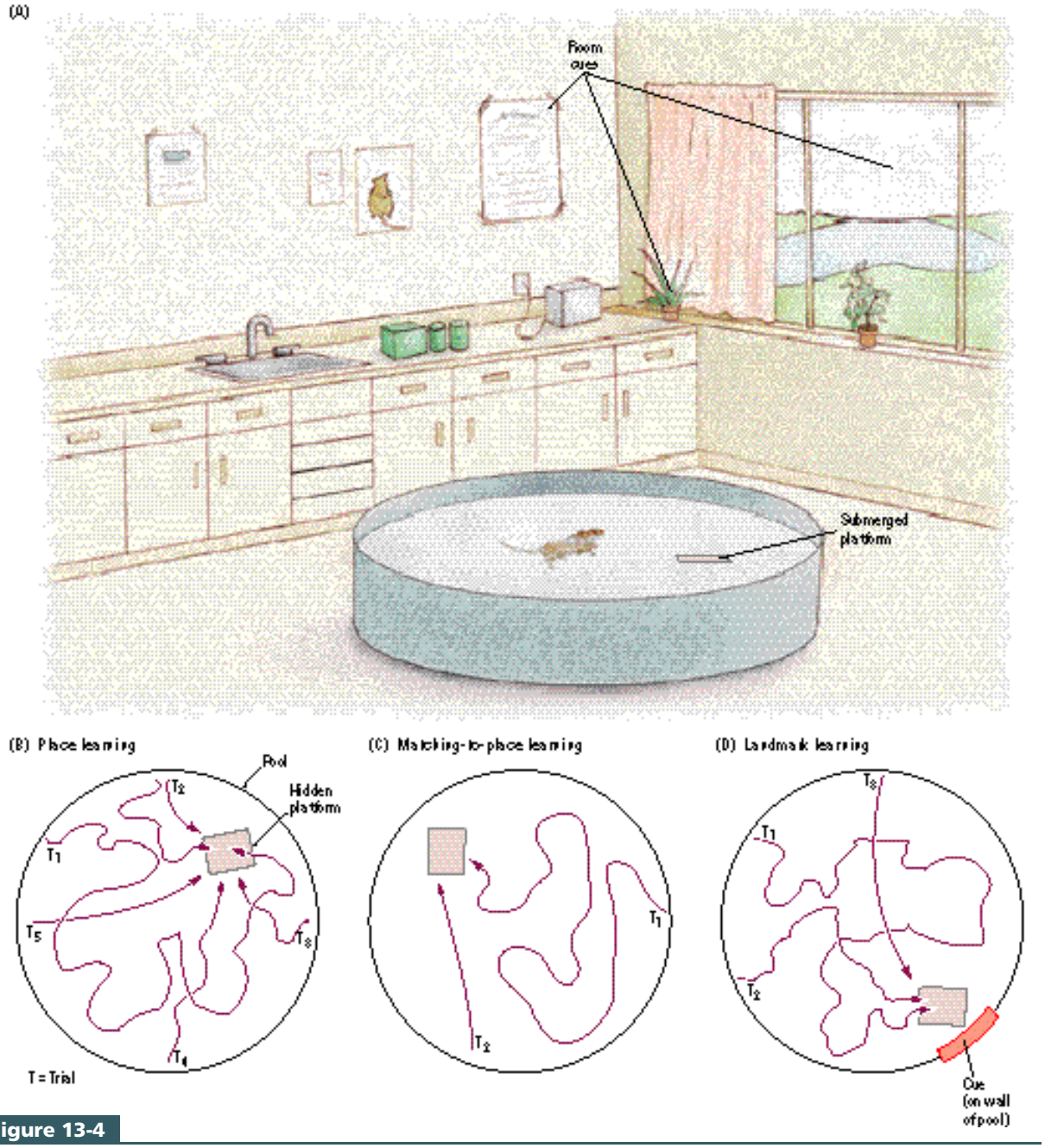


Figure 13-4

Three different visuospatial learning tasks in a swimming pool for rats. **(A)** The general arrangement of the pool. **(B)** In a place-learning task (Morris, 1981), a rat is put into the pool at various starting locations. The animal must learn the location of a hidden platform, which can be done only by considering the configuration of visual cues in the room—windows, wall decorations, potted plants, and the like. **(C)** In a matching-to-place task (Whishaw, 1989), the rat is again put in the pool at random locations, but in this case the hidden platform is in a new location each test day. The animal must learn that the location where it finds the platform on the first trial of each day is the location of the platform for all that day's trials. **(D)** In a landmark-learning task (Kolb & Walkey, 1987), the rat is required to ignore the room cues and to learn that the cue on the wall of the pool signals the location of the platform. The platform and cue are moved on each trial so that the animal is penalized for trying to use room cues to solve the problem. The red lines in **(B), (C),** and **(D)** mark the rat's swimming path on each trial (T).

In yet another variation, a cue can be placed on the wall of the pool (Figure 13-4D). The rat's task is to learn that the cue, and only the cue, indicates the approximate location of the platform. In this case, the platform moves on every trial but always maintains the same relationship to the cue, which also moves. The brain therefore is learning that all the distal cues are irrelevant and only the local cue is relevant. This is a very different task, and, once again,different neural circuitry is required to solve it.

Implicit memory. Memory in which subjects can demonstrate knowledge but cannot explicitly retrieve the information.

Explicit memory. Memory in which subjects can retrieve an item and indicate that they know the item they have retrieved is the correct item (that is, conscious memory).

Two Types of Memory

Humans present a different challenge to the study of memory because so much of our learning is verbal. Psychologists have been studying human memory since the mid-1800s, and cognitive psychologists have developed sophisticated measures of learning and memory for neuropsychological investigations. Two such measures will help us distinguish between two types of memory in humans. In one kind of task, subjects are given a list of words to read, such as *spring, winter, car*, and *boat.* Another group of subjects reads a list consisting of the words *trip, tumble, run,* and *sun.* All the subjects are then asked to define a series of words, one of which is *fall.* The word *fall* has multiple meanings, including the season and a tumble. People who have just read the word list containing names of seasons are likely to give the "season" meaning, whereas those who have read the second list will give the "tumble" meaning. Obviously, some form of unconscious (and unintentional) learning takes place as the subjects read the word lists.

This word-list task is a measure of **implicit memory.** People with **amnesia,** which is a partial or total loss of memory, perform normally on such tests of implicit memory. The amnesic person has no recollection of having read the word list, yet acts as though some neural circuit has been influenced by the list. Thus,there is a dissociation between the memory of the unconscious (or implicit) learning and the conscious recollection of training, which is referred to as **explicit memory**. This implicit–explicit distinction is not restricted to verbal learning but is true of visual learning and motor learning tasks as well. For example, subjects can be shown an incomplete sketch, such as the top panel of the Gollin figure test shown in Figure 13-5, and asked what it is. They are unlikely to be able to identify the image,so they are presented with a succession of more nearly complete sketches until they can identify the picture. When control subjects and amnesics are later shown the same sketch, both groups are able to identify the figure sooner than they could the first time. Even though the amnesic subjects may not recall having seen the sketches before,they behave as though they had.

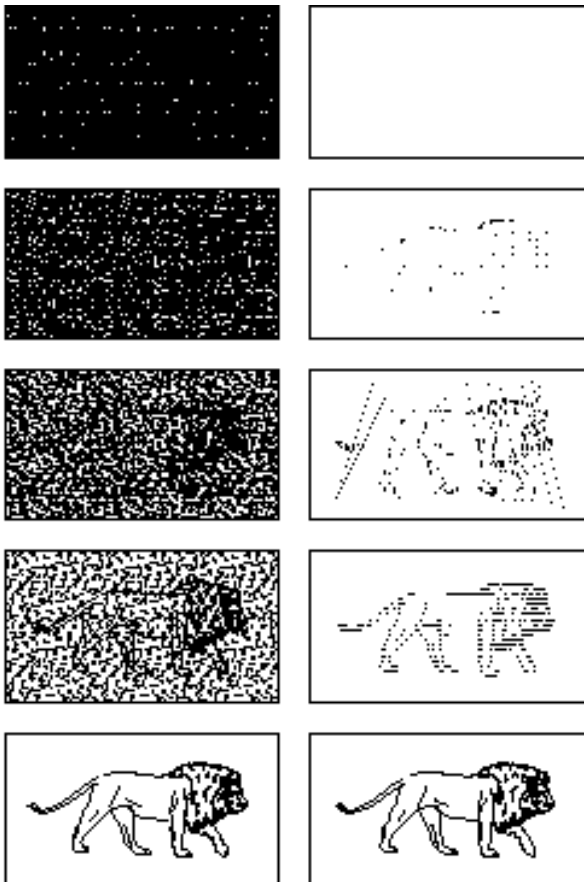
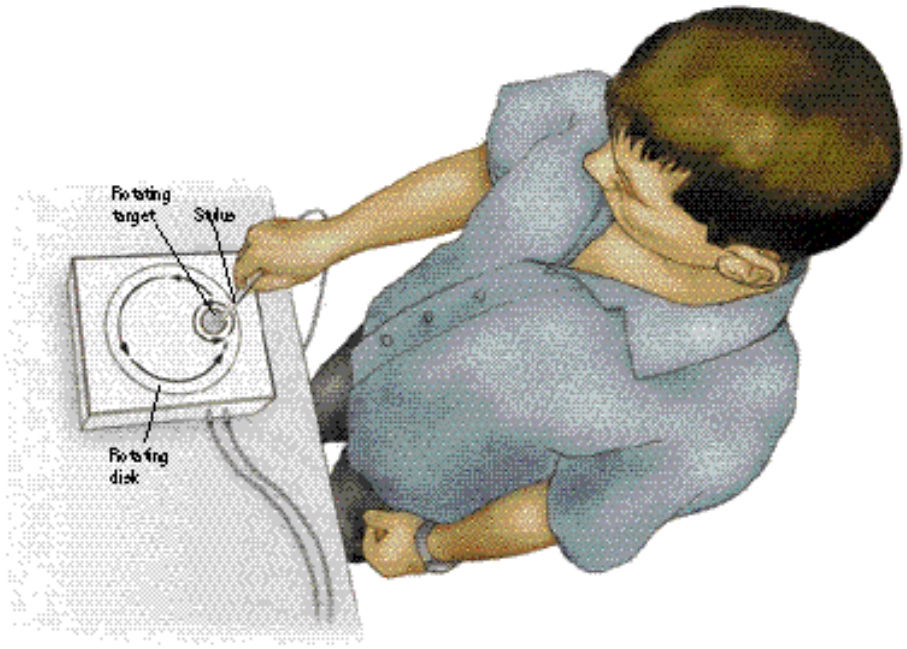


Figure 13-5

The Gollin figure test. Subjects are shown a series of drawings in sequence, from least to most clear, and asked to identify the object. It is impossible to identify the object from the first sketch, and most people must see several of the panels before they can identify the figure. On a retention test some time later, however, subjects identify the image sooner than they did on the first test, indicating some form of memory for the image. Amnesic subjects also show improvement on this test, even though they do not recall having done the test before.

Figure 13-6

The pursuit-rotor task. The subject must keep the stylus in contact with the metal disc that is moving in a circular pattern on a turntable, which is also moving in a circular pattern. Although the task is difficult, most people show significant improvement after a brief period of training. When given a second test at some later time, both normal subjects and amnesics show retention of the task. The amnesics typically do not recall having ever done the task before.



A second kind of measure reveals implicit learning of motor skills. For instance, a person can be taught some form of motor skill, such as the pursuit-rotor task shown in Figure 13-6. A small metal disc moves in a circular pattern on a turntable that is also moving. The task is to hold a stylus on the small disc as it spins. This task is not as easy as it looks, especially when the turntable is moving quickly. Nonetheless, with an hour's practice people become reasonably proficient. If they are presented with the same task a week later, both normal subjects and amnesics will take less time to perform the task. Here, too, the amnesics will fail to recall having ever done the task before. We can see, therefore, that the distinction between tests of implicit and explicit memory is consistent and must provide some key to how the brain stores information.

The distinction between implicit and explicit memory is just one way in which psychologists have categorized different memory processes. Many researchers prefer to distinguish between **declarative memory,** which refers to the specific contents of specific experiences, and **procedural memory,** which is memory of how to do something. Although some theorists may make subtle distinctions between the implicit–explicit and declarative–procedural dichotomies, there is really little practical difference and, in our view, the explicit–implicit dichotomy is the simplest one to understand. Table 13-1 lists other commonly used dichotomies, with the general distinction being that one type of memory requires the recollection of specific information whereas the other type refers to knowledge of which we are not consciously aware. We can include Pavlov's classical conditioning, Thorndike's instrumental learning, and Skinner's operant learning in this analysis, too, as they can all be considered types of implicit learning.

Table 13-1 Terms Describing Two Kinds of Memory

Term for conscious memory	Term for unconscious memory
Explicit	Implicit
Declarative	Procedural
Fact	Skill
Memory	Habit
Knowing that	Knowing how
Locale	Taxon
Cognitive mediation	Semantic
Conscious recollection	Skills
Elaboration	Integration
Memory with record	Memory without record
Autobiographical	Perceptual
Representational	Dispositional
Episodic	Semantic
Working	Reference

These pairs of terms have been used by various theorists to differentiate two forms of memory. This list is intended to help you relate other discussions of memory that you may encounter to the one in this book, which favors the explicit–implicit distinction.

Nonspeaking animals can display explicit memory. One of us owned a cat that loved to play with a little ball.One day the ball was temporarily put on a shelf to keep it away from an inquisitive 1-year-old boy. For weeks afterward the cat would sit and stare at the location where the ball had been placed. This is an explicit memory.

Animals also display explicit memory when they learn psychological tasks. Recall that in one variant of the Morris task, rats were given a new platform location on each day of training. The task therefore was to go to the platform's last location. This is an explicit piece of information, which can be demonstrably forgotten. Suppose that a well-trained rat is given one trial with the platform at a new location, and then not given a second trial for an hour, a day, 3 days, or a week. The rat has no difficulty with a delay of an hour or even a day. Some rats are flawless at 3 days, but most have forgotten the location by the time a week has elapsed. Instead,they swim around looking for the platform, which illustrates their implicit memory of the learning set, or the "rules of the game"—namely, that there is a platform and that it can be found with a certain type of search strategy.

What Makes Explicit and Implicit Memory Different?

One reason that explicit and implicit memories differ is that each type of memory is housed in a different set of neural structures. Another reason they differ is that the information is processed differently. Implicit information is encoded in very much the same way as it is perceived. This can be described as data-driven, or "bottom-up," processing. The idea is that information enters the brain by the sensory receptors and is then processed in a series of subcortical and cortical regions. For example, recall from Chapter 8 that visual information about an object goes from the visual receptors (the "bottom") to the lateral geniculate nucleus,the occipital cortex,and then the temporal lobe via the temporal stream where the object is recognized.

Explicit memory, in contrast, depends on conceptually driven, or "top-down," processing, in which the subject reorganizes the data. For example, if we were searching for a particular object such as our keys, we would ignore other objects. This is referred to as top-down because circuits in the temporal lobe (the "top") form an image that influences how incoming information is processed, which in turn greatly influences the recall of information later. Because a person has a relatively passive role in encoding implicit memory, he or she will have difficulty recalling the memory spontaneously but will recall the memory more easily when primed by the original stimulus or some feature of it. Because a person plays an active role in processing information explicitly, the internal cues that were used in processing can also be used to initiate spontaneous recall.

Studies of eyewitness testimony demonstrate the active nature of explicit memory (e.g., Loftus, 1997). In a typical experiment, people are shown a video clip of an accident in which a car collides with another car stopped at an intersection. One group of subjects is asked to estimate how fast the car was going when it "smashed" into the other car. A second group is asked how fast the car was going when it "bumped" into the other car. Later questioning indicates that the memory of how fast the first car was moving is biased by the instruction: subjects looking for "smashing" cars estimate faster speeds than those looking for "bumping" cars. In other words, the instruction causes the information to be processed differently. In both cases,the subjects were certain that their memories were accurate.

Other experiments also show that implicit memory is fallible, too. For example, subjects are read the following list of words: *sweet, chocolate, shoe, table, candy, horse,*

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car, cake, coffee, wall, book, cookie, hat. After a delay of a few minutes, the subjects hear another list of words that includes some of the words from the first list and some that are new. Subjects are asked to identify which words were present on the first list and to indicate how certain they are of the identification. One of the words on the second list is *sugar*. Most subjects indicate not just that *sugar* was on the first list but that they are *certain* that it was.Of course,it was not. This type of demonstration is intriguing, for it shows the ease with which we can form "false memories" and defend their veracity with certainty.

Although memories can be distinguished generally as implicit or explicit, the brain does not process all implicit or all explicit memories in the same way. Memories can be divided according to categories that are different from those listed in Table 13-1. For example, we can make a distinction between memories for different types of sensory information. We have seen that visual and auditory information is processed by different neural areas, so it is reasonable to assume that auditory memories are stored in different brain regions from those in which visual memories are stored. We can also make a distinction between information stored in so-called *short-term memory* and information held for a longer time in *long-term memory*. In short-term memory, information—such as the phone number of a restaurant that we have just looked up in the Yellow Pages—is held in memory only briefly, for a few minutes at most, and then is discarded. In long-term memory, information—such as a close friend's name—is held in memory indefinitely, perhaps for a lifetime. The frontal lobe plays an important role in temporary memory, whereas the temporal lobe plays a central role in long-term storage of verbal information. The crucial point is that no single place in the nervous system can be identified as the location for memory or learning. Virtually the entire nervous system can be changed with experience, but different experiences change different parts. One challenge for the experimentalist is to devise ways of manipulating experience in order to demonstrate change in different parts of the brain.

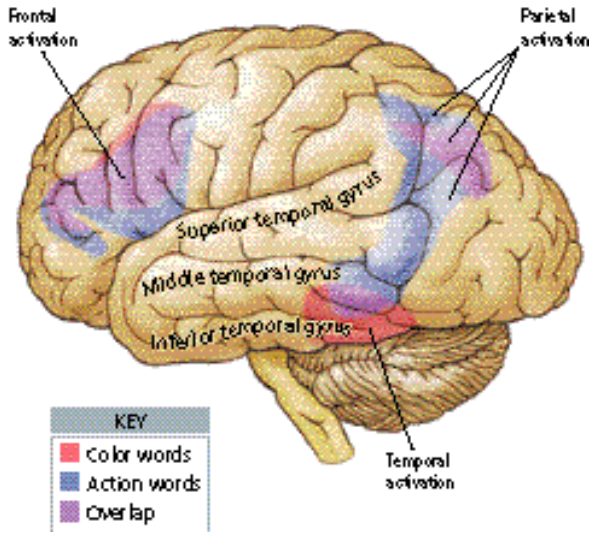
Accepting the idea that every part of the brain can learn influences our view of the nature of the neural circuits that mediate memory. For example, we could expect that areas that process information also house the memory of that information. Areas that process visual information likely will house visual memory. Because the temporal lobe has specialized regions for processing color, shape, and other visual information regarding an object's characteristics, we can predict that the memory for the visual attributes of objects will be stored separately. This prediction has been confirmed by a series of PET studies by Alex Martin and colleagues (1995) at the U.S. National Institutes of Mental Health.

In one of these studies, subjects were shown black-and-white line drawings of objects and asked to generate words denoting either colors or actions of the objects. The idea was that the processing of color and motion of objects is carried out in different locations in the temporal lobe, and thus the activity associated with the memories of color or motion might also be dissociated. In fact, just such a dissociation was demonstrated. Figure 13-7 shows that recall of colors activated a region next to the area controlling color perception, whereas recall of movement activated an area next to the area controlling the perception of motion. This distribution of activation shows not only that object memory is at least partly located in the temporal lobe but also that it is found in regions associated with the original perception of the objects.

Figure 13-7

A lateral view of the left hemisphere showing regions of increased blood flow when subjects generated color words (red) and action words (blue) in describing the visual characteristics of objects shown to them in static, black-and-white drawings. Purple indicates areas of overlap. The red region extends under the lateral portion of the temporal lobe. The generation of color words selectively activated a region in the ventral temporal lobe, just anterior to the area normally taking part in the perception of color, whereas generation of action words activated a region in the middle temporal gyrus, just anterior to the area involved in the perception of motion. These data suggest that object knowledge is organized as a distributed system in which the attributes of an object are stored close to the regions of the cortex that mediate perception of those attributes. There is also activation in the parietal lobe, which is likely related to the movements associated with actions, and in the frontal lobe, which is related to the spontaneous generation of behavior.

Adapted from "Discrete Cortical Regions Associated with Knowledge of Color and Knowledge of Action," by A. Martin, J.V. Haxby, F.M. Lalonde, C.L. Wiggs, and L.G. Ungerleider, 1995, *Science*, *270,* p. 104.



In Review

Learning is a process that results in a relatively permanent change in behavior. There are multiple forms of learning. The primary distinction can be made between Pavlovian conditioning, in which some environmental stimulus (such as a tone) is paired with a reward, and operant conditioning, in which a response (such as pushing a button) is paired with a reward. The demands on the nervous system are different in the two types of learning, so we can expect that the regions of the brain related to each learning form will be different.

Memory is the ability to recall or recognize previous experience; this implies the existence of a memory trace, or a mental representation of a previous experience. There are many forms of memory, each related to mental representations in different parts of the brain. One useful distinction is between implicit memory, in which information is unconsciously learned, and explicit memory, which is a memory for specific information. The mental representations of these forms of memory are held in different regions of the brain, as we shall see.

DISSOCIATING MEMORY CIRCUITS

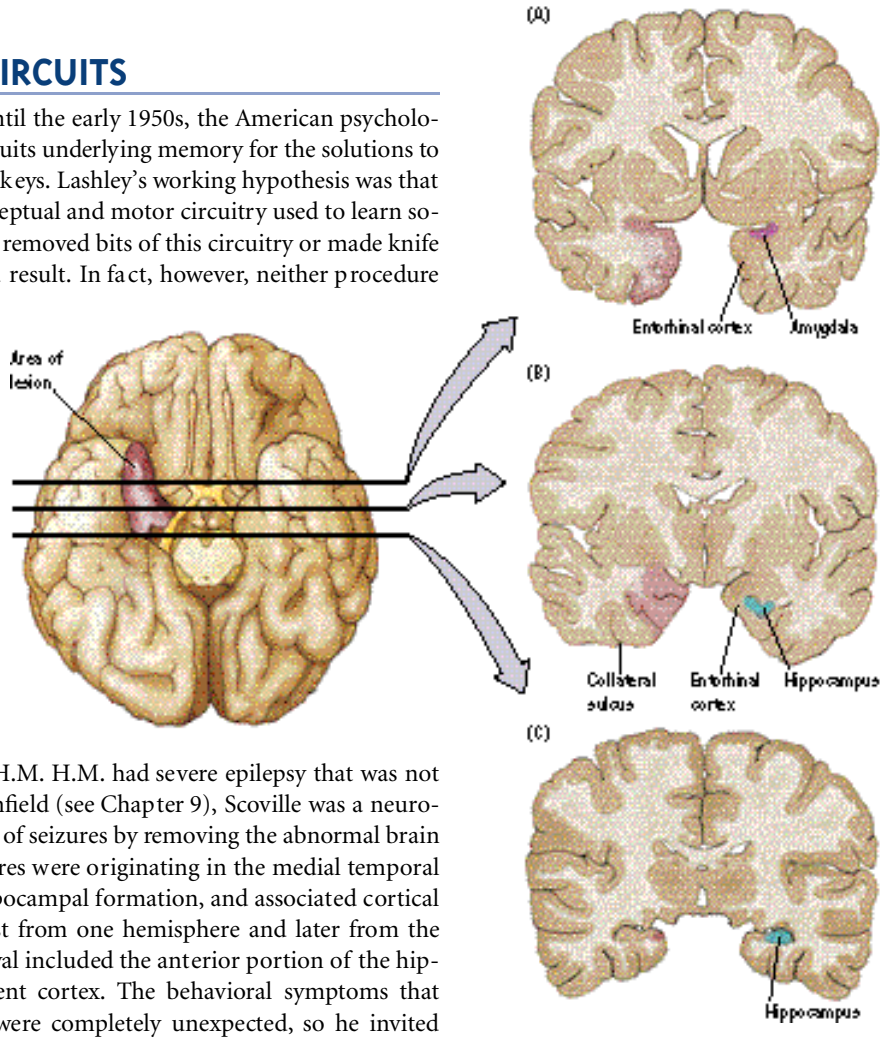
Beginning in the 1920s and continuing until the early 1950s, the American psychologist Karl Lashley looked for the neural circuits underlying memory for the solutions to mazes learned by laboratory rats and monkeys. Lashley's working hypothesis was that memories must be represented in the perceptual and motor circuitry used to learn solutions to problems. He believed that if he removed bits of this circuitry or made knife cuts that disconnected it, amnesia should result. In fact, however, neither procedure produced amnesia. What Lashley found was that the severity of the memory disturbance was related to the size of the injury rather than to its location. In 1951,after 30 years of searching, Lashley concluded that he had failed to find the location of the memory trace, although he did believe that he knew where it was *not* located (Lashley, 1960).

Ironically, it was just two years later that William Scoville made a serendipitous discovery that had not been predicted by Lashley's studies. On August 23, 1953, Scoville performed a bilateral medial temporal lobe resection on a young man who became known as Case H.M. H.M. had severe epilepsy that was not controlled by medication. Like Wilder Penfield (see Chapter 9), Scoville was a neurosurgeon who was attempting to rid people of seizures by removing the abnormal brain tissue that was causing them. H.M.'s seizures were originating in the medial temporal region, which includes the amygdala, hippocampal formation, and associated cortical structures, so Scoville removed them, first from one hemisphere and later from the other. As shown in Figure 13-8, the removal included the anterior portion of the hippocampus, the amygdala, and the adjacent cortex. The behavioral symptoms that Scoville noted after the second surgery were completely unexpected, so he invited

Figure 13-8

H.M.'s brain viewed from below, with the lesion highlighted. The right side of the brain has been left intact to show the relative location of the medial temporal structures. Because the lesion runs along the wall of the medial temporal lobe, it can be seen in several cross sections of the brain. **(A)**, **(B)**, and **(C)** depict such sections of H.M.'s brain. The drawings are based on an MRI scan of H.M.'s brain.

Adapted from "H.M.'s Medial Temporal Lobe Lesion: Findings from Magnetic Resonance Imaging," by S. Corkin, D.G. Amaral, R.G. Gonzalez , K.A. Johnson, B.T. Hyman, 1997, *Journal of Neuroscience*, 17.



Brenda Milner, one of Penfield's associates, to study H.M. Milner and her colleagues have studied H.M. for nearly 50 years, making him the most studied case in neuroscience (e.g. Milner, Corkin,& Teuber, 1968).

H.M.'s most remarkable symptom is severe amnesia: he is unable to recall anything that has happened since his surgery in 1953.H.M.still has an above-average I.Q. (118 on the Wechsler Adult Intelligence Scale), and he performs normally on perceptual tests. Furthermore, his recall of events from his childhood and school days is intact. Socially, H.M.is well mannered,and he can engage in sophisticated conversations. However, he cannot recall events that have just happened. H.M. has no explicit memory. In one study by Suzanne Corkin, H.M.was given a tray of hospital food, which he ate. A few minutes later he was given another tray. He did not recall having eaten the first meal and proceeded to eat another. A third tray was brought, and this time he ate only the dessert, complaining that he did not seem to be very hungry.

To understand the implications and severity of H.M.'s condition, one need only consider a few events in his postsurgical life. His father died, but H.M. continued to ask where his father was, only to experience anew the grief of hearing that his father had passed away. (Eventually H.M. stopped asking about his father, suggesting that some type of learning had occurred.) Similarly, when in the hospital he typically asks, with many apologies,if the nurses can tell him where he is and how he came to be there. He remarked on one occasion,"Every day is alone in itself, whatever enjoyment I've had, and whatever sorrow I've had." His experience is that of a person who perceives his surroundings but cannot comprehend the situation he is in because he does not remember what has gone before.

Formal tests of H.M.'s memory show what one would expect: he cannot recall specific information just presented. In contrast, his implicit memory performance is nearly intact. He performs normally on tests like the pursuit-rotor or incomplete-figure tasks described earlier. Whatever systems are required for implicit memory must therefore be intact, but those systems crucial to explicit memory are gone or dysfunctional. Another case, similar to that of H.M., is discussed in "Patient Boswell's Amnesia."

There are probably several reasons why Lashley did not find a syndrome like that shown by H.M. Most important,Lashley was not using tests of explicit memory, so his animal subjects would not have shown H.M.'s deficits. Rather, Lashley's tests were mostly measures of implicit memory, which H.M. has no problems with. The following case illustrates that Lashley probably should have been looking in the basal ganglia for deficits revealed by his tests.

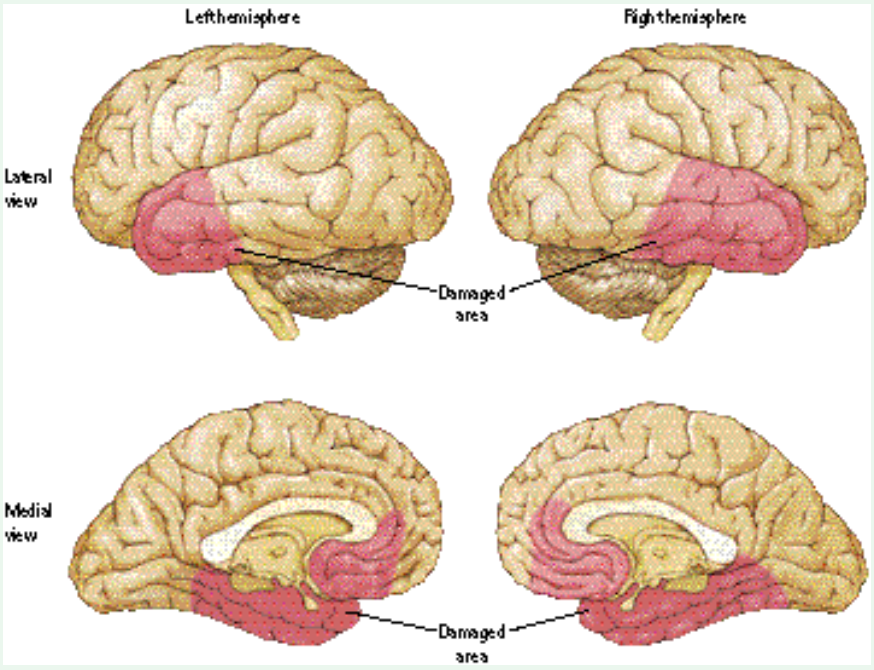
J.K.was born on June 28,1914. He was above average in intelligence and worked as a petroleum engineer for 45 years. In his mid-70s he began to show symptoms of Parkinson's disease,and at about age 78 he started to have memory difficulties.(Recall that in Parkinson's disease, the projections from the dopaminergic cells of the brainstem to the basal ganglia die.) Curiously, J.K.'s memory disturbance was related to tasks that he had done all his life. On one occasion, he stood at the door of his bedroom frustrated by his inability to recall how to turn on the lights. He remarked,"I must be crazy. I've done this all my life and now I can't remember how to do it!"On another occasion, he was seen trying to turn the radio off with the TV remote control. This time he explained, "I don't recall how to turn off the radio so I thought I would try this thing!" J.K. clearly had a deficit in implicit memory. In contrast, he was aware of daily events and could recall explicit events as well as most men his age can. He could still speak intelligently on issues of the day that he had just read about. Once when we visited him, one of us entered the room first and he immediately asked where the other was, even though it had been 2 weeks since we had told him we would be coming to visit. This intact long-term memory is very different from the situation of H.M., who

Focus on Disorders

Patient Boswell's Amnesia

Boswell is a man who, at the age of 48, developed a brain infection known as herpes simplex encephalitis. Prior to his illness, Boswell had 13 years of schooling and had worked for nearly 30 years in the newspaper advertising business. By all accounts, he was successful in his profession and was a normal, well-adjusted person. Boswell recovered from the acute symptoms of the disease, which included seizures and a 3-day coma. His postdisease intelligence was low average, probably reflecting the neurological damage caused by the disease. Nonetheless, his speech and language remained normal in every respect, and he suffered no defects of sensory perception or of movement. But Boswell was left with a profound amnesic syndrome. If he hears a short paragraph and is asked to describe the main points of the paragraph, he routinely gets scores of zero. He can only guess the day's date and is unable even to guess what year it is. When asked what city he is in, he simply guesses. He does know his place of birth, and he can correctly recall his birth date about half the time. In sum, Boswell has a profound amnesia for events both prior to and since his encephalitis. Boswell does show implicit memory, however, on tests such as the pursuit-rotor task (see Figure 13-6).

Boswell has been extensively investigated by Damasio and his colleagues (1989), and his brain pathology is now well documented. The critical damage is a bilateral destruction of the medial temporal regions and a loss of the basal forebrain and the posterior part of the orbital frontal cortex. In addition, Boswell has lost the tissue known as the insular cortex, which is found in the Sylvian fissure. In contrast, his sensory and motor cortices are intact, as are his basal ganglia. Boswell's injury is thus more extensive than H.M.'s. Like H.M., he has a loss of new memories, but, unlike H.M., he also has a severe loss of access to old information, probably because of his insular and prefrontal injuries. Nonetheless, again like H.M., Boswell has an intact procedural memory, a fact that illustrates the dissociation between neural circuits underlying explicit and implicit forms of memory.



After a herpes simplex encephalitis infection, patient Boswell suffers profound amnesia and has difficulty remembering events before and after his illness. This model highlights the areas of damage in the medial temporal region, the basal forebrain, and the posterior orbital frontal cortex.

would not have remembered that anybody was coming, even 5 minutes after being told. Because Parkinson's disease primarily affects the basal ganglia, J.K.'s deficit in implicit memory was likely related to his basal ganglia dysfunction.

In Review

In identifying the circuits responsible for memory, it is important to separate explicit memory from implicit memory. Explicit memory relies on the anterior portion of the hippocampus, the amygdala, and the adjacent cortex. These areas were damaged in H.M.'s brain, so he had no explicit memory. An implicit memory deficit indicates deterioration of the basal ganglia characteristic of Parkinson's disease, as seen in patients such as J.K.

NEURAL SYSTEMS UNDERLYING EXPLICIT AND IMPLICIT MEMORIES

Laboratory studies, largely on rats and monkeys, have shown that the symptoms of patients such as H.M. and J.K. can be reproduced in animals by injuring the medial temporal region and basal ganglia, respectively. Other structures, most notably in the frontal and temporal lobes, have also been found to play roles in certain types of explicit memory. We consider the systems for explicit and implicit memory separately.

A Neural Circuit for Explicit Memories

The dramatic amnesic syndrome discovered in H.M. in the 1950s led investigators to focus on the hippocampus, which at the time was a large anatomical structure looking for a function. However, because H.M. has damage to other structures, too, the initial view that the hippocampus was the location of explicit memory processing turned out to be incorrect. It has taken about 20 years of anatomical and behavioral studies to sort out the complexities, and only recently has a consensus begun to emerge on a theory for explicit memory. Note that if you consult books or reviews published before about 1995, the explanation may be quite different (see Gazzaniga, 2000).

The prime candidates for a role in explicit memory include the medial temporal region, the frontal cortex, and structures closely related to them. Before considering the model, we must first revisit the anatomy of the medial temporal region. As we do so, it is important to keep in mind the studies by Martin and colleagues, discussed earlier (look again at Figure 13-7). Those studies showed that memories of the color and motion characteristics of objects are in separate locations in the temporal lobe and thus that there must be multiple sensory inputs into the medial temporal region.

The macaque monkey has been the principal subject of anatomical study on the medial temporal region, and it is likely that there are few differences between macaques and humans in this respect. Three medial temporal cortical regions, in addition to the hippocampus and amygdala, take part in explicit memory. As illustrated in Figure 13-9, these regions, which lie adjacent to the hippocampus, are the **entorhinal cortex,** the **parahippocampal cortex,** and the **perirhinal cortex.** There is a sequential arrangement of connections such that the other cortical regions project to the perirhinal and parahippocampal cortices, which in turn project to the entorhinal cortex, as illustrated in Figure 13-10. The prominent input from the neocortex to the perirhinal region is from the visual regions of the ventral stream coursing through the temporal

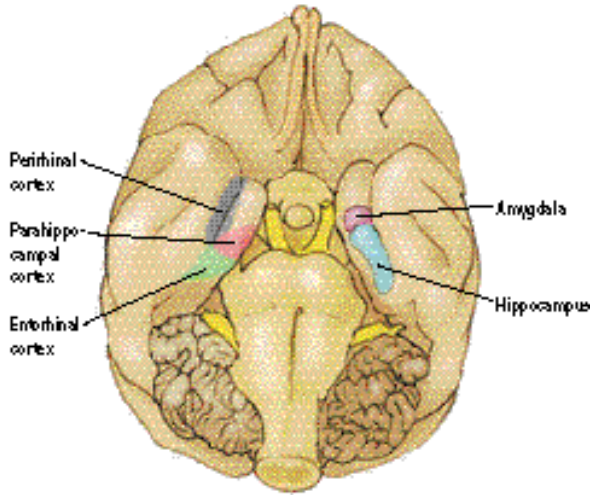


Figure 13-9

A rhesus monkey brain viewed from below, showing the medial temporal regions. On the left, three medial temporal cortical areas are shown: the perirhinal cortex (gray), the parahippocampal cortex (red), and the entorhinal cortex (green). Each of these regions plays a distinct role in processing sensory information for memory storage. On the right, the hippocampus (turquoise) and amygdala (purple) are illustrated. These last two structures are not directly visible from the surface of the brain because they lie beneath the medial temporal cortical regions illustrated on the left. Note that although these cortical and subcortical structures are illustrated on different sides of the brain, all of them are present on both sides of the brain.

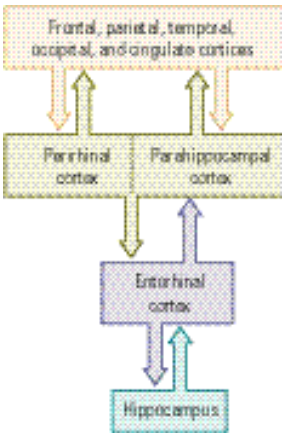


Figure 13-10

Connections among the medial temporal regions. Input from the sensory cortex flows to the parahippocampal and perirhinal regions, then to the entorhinal cortex, and, finally, to the hippocampus. The flow of sensory information is from the sensory regions to the medial temporal regions, and it then feeds back from the medial temporal regions to the sensory regions.

lobe. The perirhinal region is thus a prime candidate for visual object memory. Similarly, the parahippocampal region has a strong input from regions of the parietal cortex believed to take part in visuospatial processing. Thus,the parahippocampal region likely has a role in visuospatial memory. Because both the perirhinal and parahippocampal regions project to the entorhinal cortex, this region is likely to participate in more integrative forms of memory. Indeed, it is the entorhinal cortex that first shows cell death in **Alzheimer's disease,** which is a form of dementia characterized by severe deficits in explicit memory. (For a more detailed discussion, see "Alzheimer's Disease" on page 504.)

We are now left with a conundrum. If the hippocampus is not the key structure in explicit memory, yet is the recipient of the entorhinal connections, what does it do? The answer is that the hippocampus is probably engaged primarily in processes requiring the memory for places, such as the recall of the location of an object. This idea was first advanced by John O'Keefe and Lynn Nadel in 1978. Certainly, both laboratory animals and human patients with selective hippocampal injury have severe deficits in various forms of spatial memory. For example, rats with hippocampal damage have great difficulty solving spatial navigation tasks such as those shown in Figure 13-4.

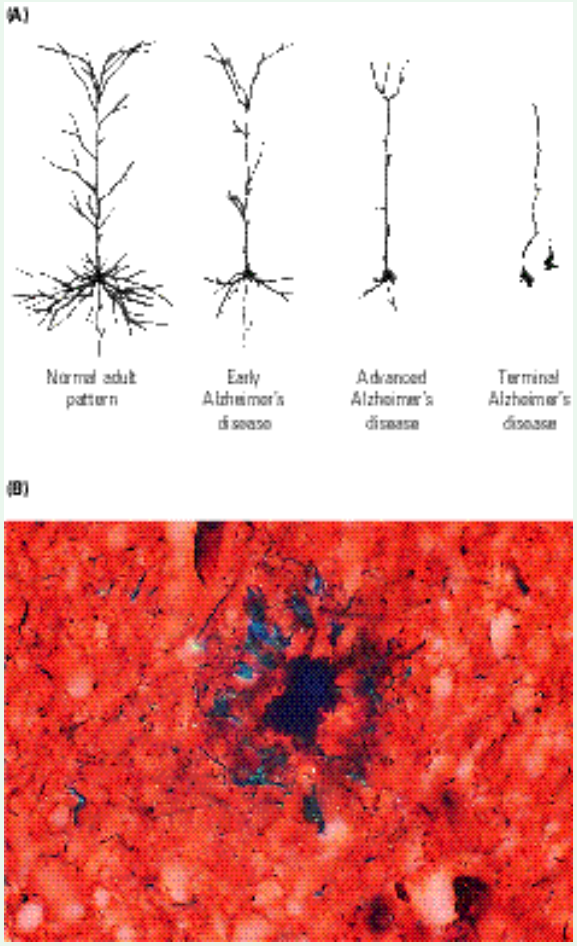
Focus on Disorders

Alzheimer's Disease

It was noted in the 1880s that the brain undergoes atrophy with aging, but the reason was not really understood until the German physician Alois Alzheimer published a landmark study in 1906. Alzheimer reported on a 51-year-old woman for whom he described a set of behavioral symptoms and associated neuropathology. In particular, the woman was demented and had various abnormalities in the cellular structure of the cerebral cortex, including both the neocortex and the limbic cortex. An estimated 1 million people now are affected by Alzheimer's disease in the United States, although the only certain diagnostic test is postmortem examination of cerebral tissue. The disease progresses slowly, and many people with Alzheimer's disease probably die from other causes before the cognitive symptoms become incapacitating. We knew of a physics professor who continued to work until he was nearly 80 years old, at which time he succumbed to a heart attack. Postmortem examination of his brain revealed significant Alzheimer's pathology. His slipping memory had been attributed by his colleagues to a case of "old-timer's disease."

The cause of Alzheimer's disease remains unknown, although it has been variously attributed to genetic predisposition, abnormal levels of trace elements, immune reactions, and slow viruses. Two principal neuronal changes occur in Alzheimer's disease. First, there is a loss of cholinergic cells in the basal forebrain. One type of treatment for Alzheimer's, therefore, is to provide medication to increase cholinergic levels in the forebrain. An example is Cognex, which is the trade name for tacrine hydrochloride, a cholinergic agonist that appears to provide temporary relief from the progression of the disease.

The second pathology is the development of neuritic plaques in the cerebral cortex. The plaques consist of a central core of homogeneous protein material known as amyloid, surrounded by degenerative cellular fragments. The cortical plaques are not distributed evenly throughout the cortex but are concentrated especially in the temporal-lobe areas related to memory. Cortical neurons begin to deteriorate as the cholinergic loss and plaques develop, as illustrated here. The first cells to die are in the entorhinal cortex, and significant memory disturbance ensues.



Cecil Fox/Science Source/Photo Researchers

As Alzheimer's disease progresses, neurons begin to deteriorate. (*Top*) These cortical pyramidal cells illustrate the progression of the disease. (*Bottom*) The neuritic plaque often found in the cerebral cortices of Alzheimer's patients. The plaque, which is the dark spot in the center of the image, is surrounded by the residue of degenerated cells.

Part (A) drawn from Golgi-stained sections. After "Age-Related Changes in the Human Forebrain," by A. Scheibel, *Neuroscience Research Program Bulletin,* 1982, *20,* pp.577–83.

Similarly, monkeys with hippocampal lesions have difficulty learning the location of objects. This can be demonstrated in tasks such as those illustrated in Figure 13-11. Monkeys are trained to displace objects to obtain a food reward (Figure 13-11A).Once they have learned how to do this, they are given one of two tasks. In the first task, shown in Figure 13-11B, known as a *visual-recognition task*, the animal displaces a sample object to obtain a food reward. After a short delay, the animal is presented with two objects, one of which is novel. The task is to learn that the novel object must be displaced in order to obtain a food reward. This is a test of explicit visual object memory. In the second task, shown in Figure 13-11C,the monkey is shown one object, which is displaced for a food reward. Then the monkey is shown the same object along with a second, identical one. The task is to learn that the object that is in the same position as it was in the initial presentation must be displaced. Monkeys with hippocampal lesions are selectively impaired at this object-position task. (Monkeys with perirhinal lesions are impaired at the object-recognition task.)

From these studies on the hippocampus, we would predict that animals with especially good spatial memories should have bigger hippocampi than do species with poorer spatial memories. David Sherry and his colleagues (1992) tested this hypothesis in birds. Many birds will take food items, such as sunflower seeds,and hide them for later consumption. Some birds can find hundreds of items that they have cached. To evaluate whether the hippocampus plays a role in this activity, Sherry and his coworkers measured hippocampal size in bird species that are closely related but only one of which is a food cacher. As shown in Figure 13-12,the hippocampal formation is larger in birds that cache food than in birds that do not. In fact, the hippocampus of food-storing birds is more than twice as large as expected for birds of their brain size and body weight. Sherry found a similar relationship when he compared different species of food-storing rodents. Rodents such as Merrian's kangaroo rat, which stores food in various places around its territory, have larger hippocampi than do rodents such as the bannertail kangaroo rat, which stores food only in its burrow. Hippocampal size in both birds and mammals appears to be related to the cognitive demands of foraging and food storing, which are highly spatial activities.

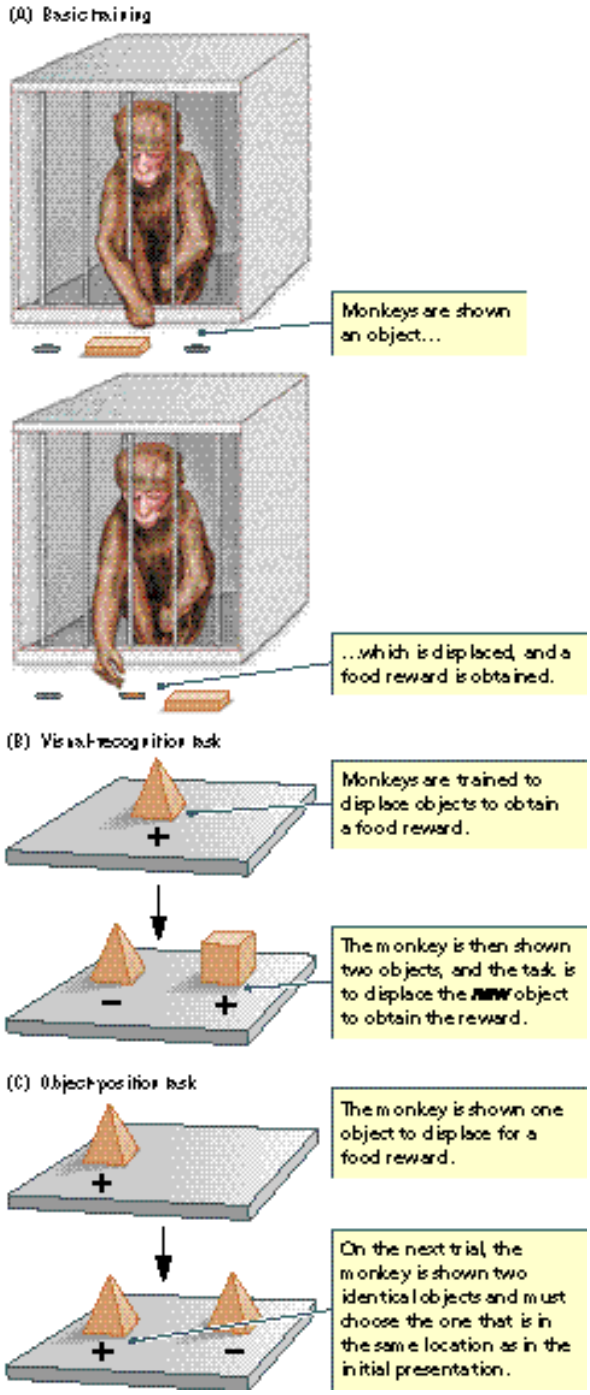


Figure 13-11

Two memory tasks for monkeys. **(A)** The monkey is shown an object, which is displaced to obtain a food reward. **(B)** A visual-recognition task. After a brief delay, the monkey is shown two objects and the task is to displace the novel object to obtain the reward. The monkey must retain the explicit information regarding which object was just seen. **(C)** An object-position task. The monkey is shown one object, which is displaced for a food reward. The monkey is then shown the same object plus a second, identical object. The task is to choose the object that is in the same location as in the first presentation. The + and – indicate whether the object is (+) or is not (–) associated with food.

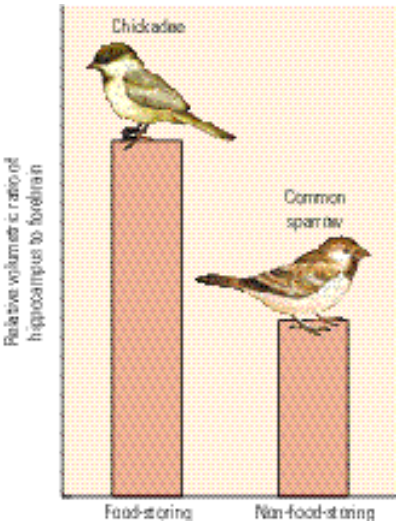


Figure 13-12

The volume of the hippocampus relative to the volume of the forebrain in three food-storing and ten non-food-storing families of passerine birds. The hippocampus of food-storing birds, such as the black-capped chickadee, is about twice as large as the hippocampus of non-food-storing birds, such as the sparrow.

Data from "Spatial Memory and Adaptive Specialization of the Hippocampus," by D.F. Sherry, L.F. Jacobs, and S.J.C. Gaulin, 1992, *Trends in Neuroscience, 15,* pp.298–303.

One prediction that we might make from the Sherry experiments is that people who have jobs with high spatial demands might have large hippocampi. Taxi drivers in London fit this category. In order to qualify for a cab driver's license in London, candidates must pass an extensive exam in which they must demonstrate that they know the location of every street in that huge and ancient city. Eleanor Maguire and her colleagues (2000), using magnetic resonance imaging (MRI), found the posterior region of the hippocampus in London taxi drivers to be significantly larger than in the control subjects. This finding presumably explains why this select group is able to pass a spatial memory test that most of us would fail miserably.

One key feature of the medial temporal pathway of explicit memory is that it is reciprocal. That is, the connections from the neocortex run to the entorhinal cortex and then back to the neocortex. These reciprocal connections have two benefits. First, the signals that the medial temporal regions send back to the cortical sensory regions keep the sensory experience alive in the brain. This means that the neural record of an experience outlasts the actual experience. Second, the pathway back to the cortex means that the neocortex is kept apprised of information being processed in the medial temporal regions. We shall see that such feedback does not happen in the basal ganglia systems taking part in implicit memory, which may help to explain the unconscious nature of implicit memory.

Although we have focused on the role of the medial temporal regions,other structures are also important in explicit memory. People with frontal-lobe injuries are not amnesic like H.M. or J.K., but they do have difficulties with memory for the temporal order of events. Imagine that you are shown a series of photographs and asked to remember them. A few minutes later, you are asked whether you recognize two photographs and,if so, to indicate which one you saw first. H.M. would not remember the photographs. People with frontal-lobe injuries would recall seeing the photographs but would have difficulty recalling which one they had seen most recently. The role of the frontal lobe in explicit memory is clearly more subtle than that of the medial temporal lobe. But just what is that role?

All the sensory systems in the brain send information to the frontal lobe,as do the medial temporal regions. This information is not used for direct sensory analysis,so it must have some other purpose. In general,it appears that the frontal lobe has a role in many forms of short-term memory. Over the past 30 years, Joaquin Fuster (e.g., Fuster et al.,2000) has studied single-cell activity in the frontal lobe during short-term memory tasks. For example,if monkeys are shown an object that they must remember for a short time before being allowed to make a response, neurons in the prefrontal cortex will show a sustained firing during the delay. Consider the tests illustrated in Figure 13-13. A monkey is shown a light, which is the cue, and then must make a response after a delay. In the delayed-response task, the monkey is shown two lights in the choice test and must choose the one that is in the same location as the cue. In the delayed-alternation task,the monkey is again shown two lights in the choice tests but now must choose the light that is *not* in the same location as the cue. Finally, in the delayed-matching-to-sample task,the monkey is shown,say, a red light,and then after a delay is shown a red and a green light. The task is to choose the red light. Fuster has found that in each task, there are cells in the prefrontal cortex that will fire throughout the delay. Animals that have not learned the task show no such cell activity. Curiously, if a trained animal makes an error, the activity of the cells reflects it:the cells stop responding before the error occurs. In a real sense,the cell has "forgotten" the cue.

There is one form of explicit memory disturbance that we have not yet described. People who have chronically abused alcohol develop a disorder known as **Korsakoff's syndrome.** Such people have severe deficits in explicit memory and, in some cases,implicit memory as well. This syndrome is caused by a thiamine (vitamin B_1) deficiency

Korsakoff's syndrome. A permanent loss of the ability to learn new information (anterograde amnesia) caused by diencephalic damage resulting from chronic alcoholism or malnutrition that produces a vitamin B_1 deficiency.

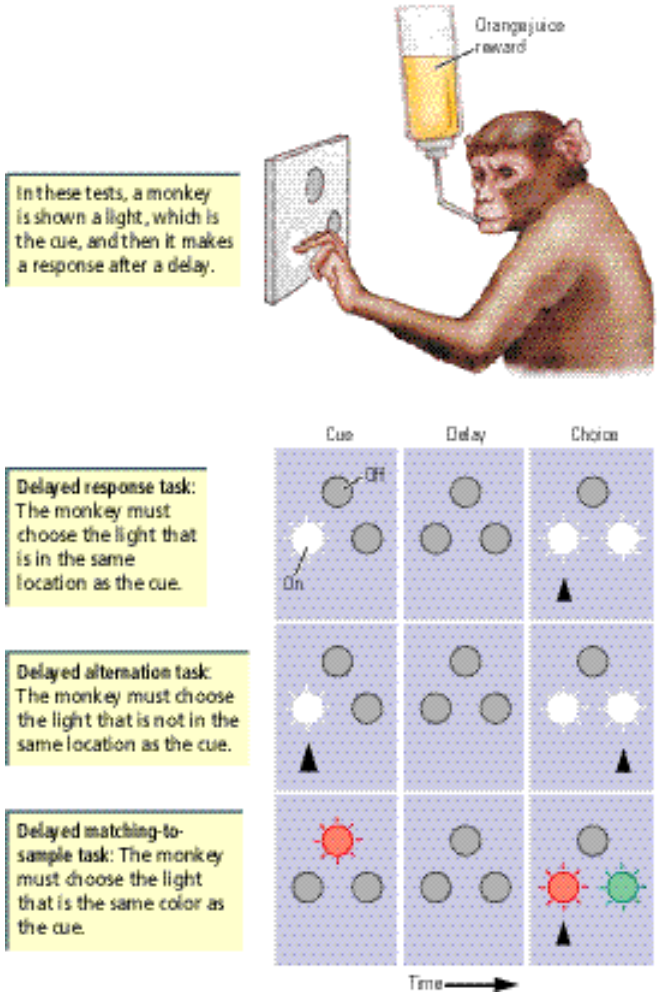


Figure 13-13

(*Top*) A monkey performing a short-term memory task. A disc lights up and the animal responds by pressing the disc in order to get a fruit juice reward. After a delay, the two lower discs are illuminated. The monkey must press the appropriate disc to obtain a reward. (The correct disc varies, depending on the requirements of the task.) (*Bottom*) Three different short-term delay tasks. The correct disc is indicated by the arrow in each case.

Adapted from *Memory in the Cerebral Cortex,* p. 178, by J. Fuster, 1995, Cambridge, MA: MIT Press.

that results from poor nutrition and the fact that alcohol inhibits the body's ability to absorb vitamin B_1. The effect of the B_1 deficiency is to produce cell death in the medial part of the diencephalon, including the medial thalamus and mammillary bodies of the hypothalamus. In addition, 80 percent of Korsakoff patients have atrophy (loss of cells) of the frontal lobes. The memory disturbance is probably so severe in many Korsakoff patients because the damage includes not only the frontal lobe but medial temporal structures as well. (This syndrome is discussed further in "Korsakoff's Syndrome" on page 509.)

Mort Mishkin and his colleagues (Mishkin, 1982; Murray, 2000) at the U.S. National Institutes of Mental Health have proposed a circuit for explicit memory that incorporates the evidence from both humans and laboratory animals with injuries to the temporal and frontal lobes. Figure 13-14 presents a modified version of the Mishkin model that includes not only the frontal and temporal lobes but also the medial thalamus, which is implicated in Korsakoff's syndrome, as well as the ascending systems from the basal forebrain, which are implicated in Alzheimer's disease. The sensory neocortical areas send their connections to the medial temporal regions, which are in turn connected to the medial thalamus and prefrontal cortex. The basal forebrain structures are hypothesized to play a role in the maintenance of appropriate levels of activity in the forebrain structures so that they can process information. The

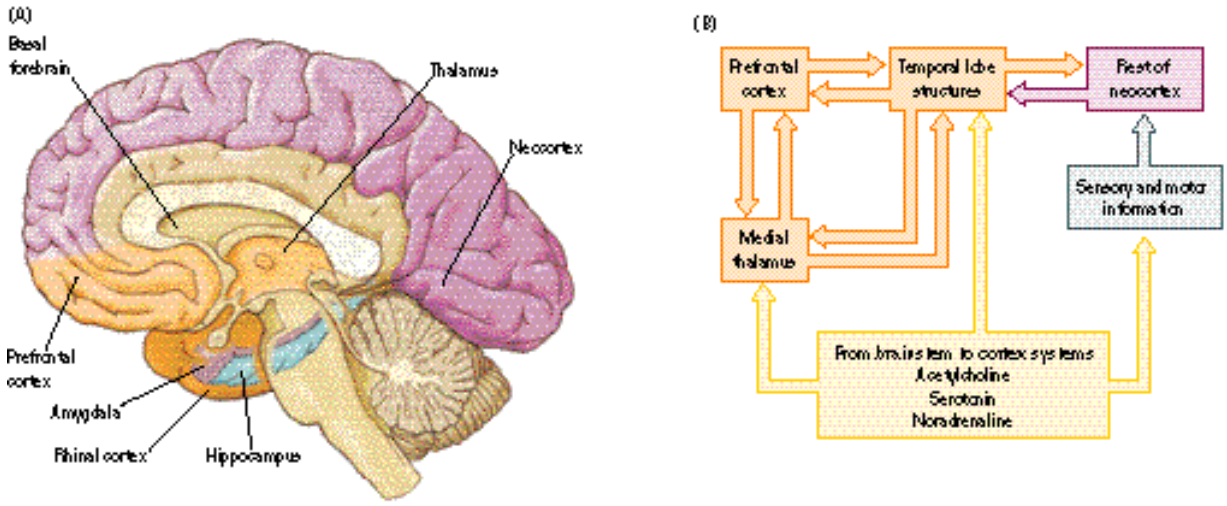


Figure 13-14

A neural circuit proposed for explicit memory. **(A)** The general anatomical areas of explicit memory. **(B)** A circuit diagram showing the flow of information through the circuits. Information flow begins with inputs from the sensory and motor systems, which themselves are not considered part of the circuit.

temporal-lobe structures are hypothesized to be central to the formation of long-term explicit memories, whereas the prefrontal cortex is central to the maintenance of temporary (short-term) explicit memories as well as memory for the recency (that is, the chronological order) of explicit events.

A Neural Circuit for Implicit Memories

Mishkin and his colleagues (1982, 1997) have also proposed a circuit for implicit memories, hypothesizing that the basal ganglia are central to implicit memory. As Figure 13-15 shows, the basal ganglia receive input from the entire cortex. The basal ganglia send projections to the ventral thalamus and then to the premotor cortex. The basal ganglia also receive projections from cells in the substantia nigra. These projections contain the neurotransmitter dopamine, which is widely and densely distributed to the basal ganglia. Dopamine appears to be necessary for circuits in the basal ganglia to function, so it may indirectly participate in implicit memory formation.

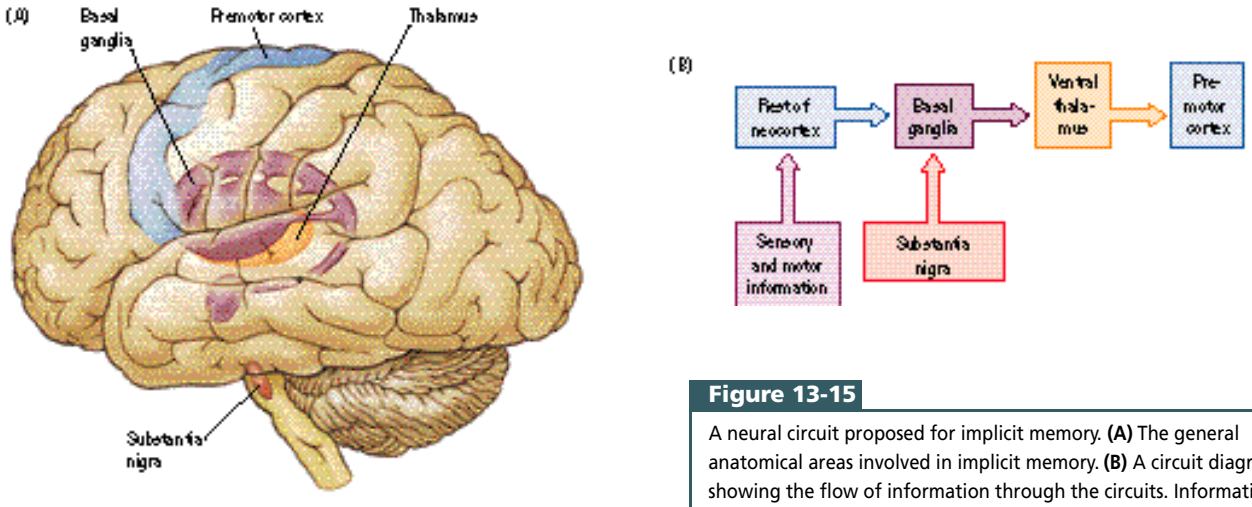


Figure 13-15

A neural circuit proposed for implicit memory. **(A)** The general anatomical areas involved in implicit memory. **(B)** A circuit diagram showing the flow of information through the circuits. Information flow begins with inputs from the sensory and motor systems, which themselves are not considered part of the circuit.

Focus on Disorders

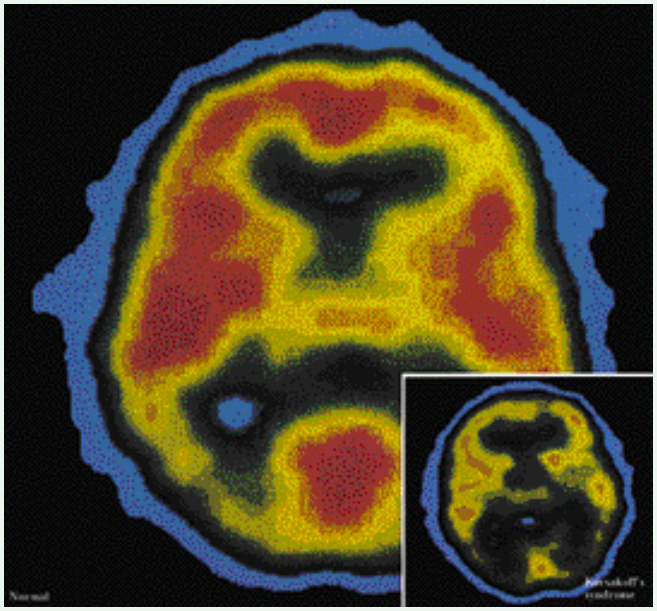
Korsakoff's Syndrome

Long-term alcoholism, especially when accompanied by malnutrition, has long been known to produce defects of memory. Joe R. was a 62-year-old man who was hospitalized because his family complained that his memory had become abysmal. His intelligence was in the average range, and he had no obvious sensory or motor difficulties. Nevertheless, he was unable to say why he was in the hospital and usually stated that he was actually in a hotel. When asked what he had done the previous night, he typically would say that he "went to the Legion for a few beers with the boys." Although he had, in fact, been in the hospital, it was a sensible response because that is what he had done on most nights over the previous 30 years. Joe R.was not certain what he had done for a living but believed that he had been a butcher. In fact, he had been a truck driver for a local delivery firm. His son was a butcher, however, so once again his story was related to something in his life. His memory for immediate events was little better. On one occasion, we asked him to remember having met us, and then we left the room. Upon our return 2 or 3 minutes later, he had no recollection of having ever met us or of having taken psychological tests administered by us.

Joe R. had Korsakoff's syndrome, a condition named after Sergei Korsakoff, a Russian physician who in the 1880s first called attention to a syndrome that accompanies chronic alcoholism. The most obvious symptom is severe loss of memory, including amnesia for both information learned in the past (retrograde amnesia) and information learned since the onset of the memory disturbance (anterograde amnesia). One unique characteristic of the amnesic syndrome in Korsakoff patients is that they tend to make up stories about past events, rather than admit that they do not remember. Like those of Joe R., however, these stories are generally plausible because they are based on actual experiences.

Curiously, Korsakoff patients have little insight into their memory disturbance and are generally indifferent to suggestions that they have a memory problem. In fact, such patients are generally apathetic to things going on around them. Joe R. was often seen watching television when the set was not turned on.

The cause of Korsakoff's syndrome is a thiamine (vitamin B_1) deficiency resulting from prolonged intake of large quantities of alcohol. Joe R. had a long history of drinking a 26-ounce bottle of rum every day, in addition to a "few beers with the boys." The thiamine deficiency results in the death of cells in the midline diencephalon, including especially the medial regions of the thalamus and the mammillary bodies of the hypothalamus. The majority of Korsakoff patients also show cortical atrophy, especially in the frontal lobe. Once the Korsakoff symptoms appear, which can happen quite suddenly, prognosis is poor. Only about 20 percent of patients show much recovery after a year on a vitamin B_1–enriched diet. Joe R. has shown no recovery after several years and will spend the rest of his life in a hospital setting.



Courtesy Dr. Peter R. Martin from *Alcohol Health & Research World*, Spring 1985, 9, cover.

These PET scans from a normal patient (the larger image) and a patient suffering from Korsakoff's syndrome (the inset) demonstrate reduced activity in the frontal lobe of the diseased brain. (The frontal lobes of the brains shown are at the bottom center of each photo.) Red and yellow represent areas of high metabolic activity versus the lower level of activity in the darker areas.

The connection from the cortex to the basal ganglia in the implicit memory system is unidirectional. Thus, most of the neocortex receives no direct information regarding the activities of the basal ganglia. Mishkin believes that this accounts for the unconscious nature of implicit memories. In order for memories to be conscious, there must be direct feedback to the neocortical regions involved. (Recall that in the explicit memory system, the medial temporal regions send connections back to the neocortical regions.)

Review the locations of the basal ganglia on the CD-ROM in the module on the Central Nervous System.

Mishkin's model shows why people with dysfunction of the basal ganglia, as in Parkinson's disease, have deficits in implicit memory, whereas people with injuries to the frontal or temporal lobes have relatively good implicit memories, even though they may have profound disturbances of explicit memory. In fact, some people with Alzheimer's disease are able to play games expertly even though they have no recollection of having played them before. Daniel Schacter (1983) wrote of a golfer with Alzheimer's disease who retained his ability to play golf, despite some impairment of his explicit knowledge of the events of having played a round,as indexed by his inability to find shots or to remember his strokes on each hole. This man's medial temporal system was severely compromised by the disease, but his basal ganglia were unaffected.

A Neural Circuit for Emotional Memories

We have not yet considered a third type of memory, which we can label *emotional memory.* It is not altogether clear whether emotional memories are implicit or explicit; in fact,it seems that they could be both. Certainly, people can react with fear to specific stimuli that they can identify; we have seen that they can also have fear of situations for which they do not seem to have specific memories. Indeed, one common pathology is a panic disorder in which people show marked anxiety but cannot identify a specific cause. For this reason, we see emotional memory as a special form of memory. This form of memory also has a unique anatomical component, namely the amygdala, which we discussed in detail in Chapter 11, where we noted that the amygdala seems to be responsible for our feelings of anxiety toward stimuli that by themselves would not normally produce fear. The amygdala has connections to systems that control autonomic functions (for example, blood pressure and heart rate) as well as connections to the hypothalamus and its control of hormonal systems.

Emotional memory has been studied most thoroughly by pairing noxious stimuli, such as foot shock, with a tone (see Figure 13-2). Michael Davis (1992) and Joseph LeDoux (1995) used this type of experiment to demonstrate that the amygdala is critical to this form of memory. Damage to the amygdala abolishes emotional memory but has little effect on implicit or explicit memory. The amygdala has close connections with the medial temporal cortical structures, as well as the rest of the cortex, and it sends projections to structures involved in the production of autonomic responses, namely the hypothalamus and central gray of the brainstem (Figure 13-16). In addition, the amygdala is connected to the implicit system via its connections with the basal ganglia.

Fear is not the only type of emotional memory that is coded by the amygdala. A study of severely demented patients by Bob Sainsbury and Marjorie Coristine (1986) nicely illustrates this point. The patients were believed to have severe cortical abnormalities but intact amygdalar functioning. The researchers first established that the ability of these patients to recognize photographs of close relatives was severely impaired. The patients then were shown four photographs, one of which depicted a relative (either a sibling or a child) who had visited in the past 2 weeks. The task was to identify the person that they liked better than the others. Although the subjects were unaware that they knew anyone in the group of photographs, they consistently pre-

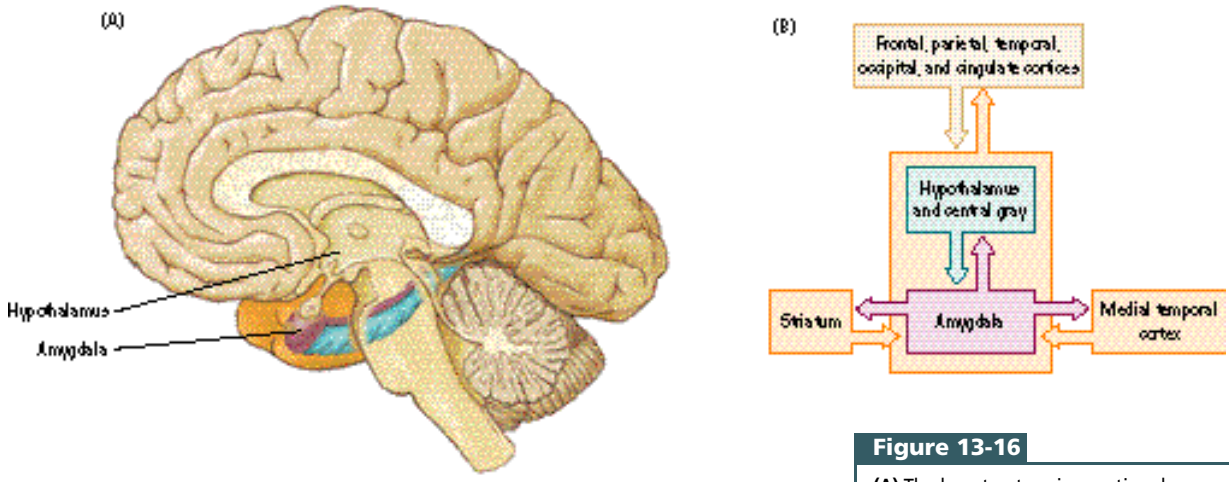


Figure 13-16

(A) The key structure in emotional memory is the amygdala. **(B)** A circuit diagram showing the flow of information in emotional memory.

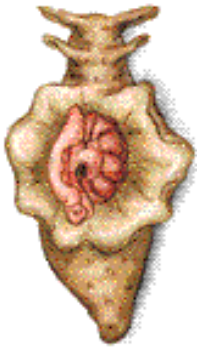
ferred the photographs of their relatives. This result suggests that although the explicit, and probably implicit, memory of the relative was gone,each patient still had an emotional memory that guided his or her preference.

In Review

Certain neural structures and circuits are associated with different types of learning and memory. One system, consisting of the prefrontal cortex and the medial temporal lobe and regions related to them, is the likely neural location of explicit memory. A second system, consisting of the basal ganglia and neocortex, forms the neural basis for implicit memory. A third system, which includes the amygdala and its associated structures, forms the neural basis for emotional memory. Presumably, when we learn different types of information, changes take place in synapses in these systems, and these changes produce our memory of the experience. We now turn to the question of what these synaptic changes might be.

THE STRUCTURAL BASIS OF BRAIN PLASTICITY

We have seen that there are different types of memory and that different brain circuits underlie each memory type. Our next task is to consider how the neurons in these circuits change to store the memories. The consensus among neuroscientists is that the changes occur at the synapse, in part because that is where neurons influence one another. This idea is not new, dating back to 1928, when the Spanish anatomist Santiago Ramón y Cajal suggested that the process of learning might produce prolonged morphological changes in the efficiency of the synapses activated in the learning process. This idea turned out to be easier to propose than to study. The major challenge that researchers still encounter as they investigate Cajal's suggestion is that they have to know where in the brain to look for synaptic changes that might be correlated with memory for a specific stimulus. This task is formidable. Imagine trying to find the exact location of the neurons responsible for storing your grandmother's name.We would have a similar problem in finding the neurons responsible for the memory of an object as a monkey performs the visual-recognition task illustrated in Figure 13-11.



Aplysia

Investigators have approached the problem of identifying synaptic change in two distinctly different ways. The first is to study relatively simple neural systems. Recall from Chapter 5 that the study of *Aplysia* revealed that changes occur in the properties of the synapse when animals learn the association between a noxious stimulus and a cue signaling the onset of the stimulus. Similarly, we saw that synaptic changes occur in hippocampal slices in which long-term enhancement (LTE) is induced. The identification of synaptic change is possible in *Aplysia* and LTE because we know where in the nervous system to look. But we have little information about where to look for memory-storing synapses in mammals.

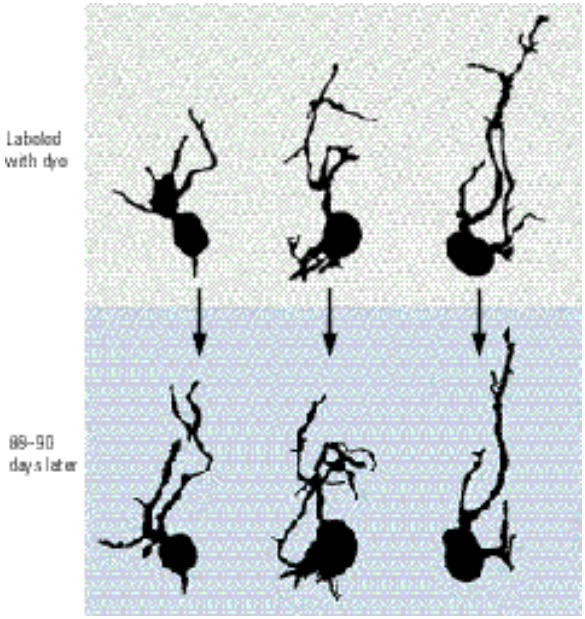
Accordingly, a second approach to finding the neural correlates of memory aims to determine that synaptic changes are correlated with memory in the mammalian brain. The next step is to localize the synaptic changes to specific neural pathways. Then the task is to analyze the nature of the synaptic changes themselves.

The goal of this section of the chapter is to describe the studies that have identified the presence of synaptic changes correlated with various types of experience. We first consider the general research strategy. We then look at the gross neural changes correlated with different forms of experience, ranging from living in specific environments, to learning specific tasks or having specific experiences, to the chronic administration of trophic factors, hormones, and addictive drugs. We shall see that the general synaptic organization of the brain is modified in a strikingly similar manner with each of these quite diverse forms of experience.

Figure 13-17

Reconstructions of portions of the dendrites of three mouse superior cervical ganglion cells observed at an interval of 3 months. Changes in both the extension and retraction of particular dendritic branches are evident.

Adapted from "Imaging Mammalian Nerve Cells and Their Connections over Time in Living Animals," by D. Purves and J.T. Voyvodic, *Trends in Neuroscience*, 1987, *10,* p. 400.



Measuring Synaptic Change

In principle, experience could alter the brain in either of two ways: by modifying existing circuitry or by creating novel circuitry. In actuality, the brain uses both of these strategies.

MODIFYING EXISTING CIRCUITS

The simplest way to look for synaptic change is to look for gross changes in the morphology of dendrites. Dendrites are essentially extensions of the neuron membrane that are present to allow more space for synapses. Because complex neurons, such as pyramidal cells, have 95 percent of their synapses on the dendrites, measurement of the changes in dendritic extent can be used to infer synaptic change. Cells that have few or no dendrites have limited space for inputs, whereas cells with complex dendritic structure have space for tens of thousands of inputs. More dendrites mean more connections, and fewer dendrites mean fewer connections. Change in dendritic structure, therefore, implies change in synaptic organization.

A striking feature of dendrites is that their shape is highly changeable. Dale Purves and his colleagues (Purves & Voyvodic, 1987) labeled cells in the dorsal-root ganglia of living mice with a special dye that allowed them to visualize the cells' dendrites. As shown in Figure 13-17, when they examined the same cells at intervals ranging from a few days to weeks, they identified obvious qualitative changes in dendritic extent. We can assume that new dendritic branches have new synapses and that lost branches mean lost synapses. One obvious lesson from the Purves studies is that the morphology of neurons is not static. Instead, neurons change their morphology in response to their changing experiences. Researchers can take advantage of this changeability as they search for

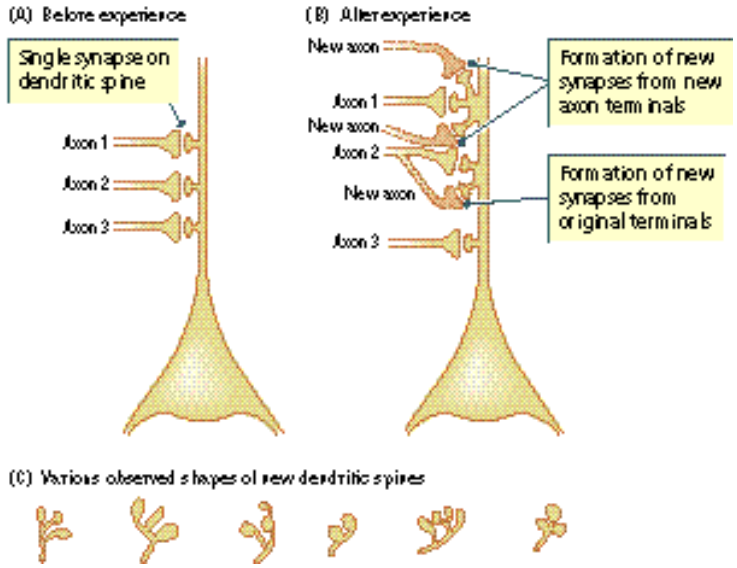


Figure 13-18

(A) Three inputs to a dendrite of a pyramidal cell. Each axon forms a synapse with a different dendritic spine. **(B)** The formation of multiple spine heads. The original axons may divide and innervate two spine heads, or new axons (dotted outlines) may innervate the new spine heads. **(C)** Drawings of multiple spine heads, showing that single dendritic spines may have multiple synapses.

neural correlates of memory by studying the changes in dendritic morphology that are correlated with specific experiences, such as the learning of some task.

What do changes in dendritic morphology actually reveal? Let us consider the case in which a given neuron generates more synaptic space. The new synapses that are formed can be either additional synapses between neurons that were already connected with the neuron in question or synapses between neurons that were not previously connected. Examples of these distinctly different synapse types are illustrated in Figure 13-18. New synapses can result either from the growth of new axon terminals or from the formation of synapses along axons as they pass by dendrites. In both cases, however, the formation of new synapses reflects changes in the local circuitry of a region and not the development of new connections between distant parts of the brain. Forming new connections between widely separated brain regions would be very difficult in a fully grown brain because of the dense plexus of cells, fibers,and blood vessels that lies in the way. Thus, the growth of new synapses indicates modifications to basic circuits that are already in the brain. This point has an important implication for the location of synaptic changes underlying memory. During development, the brain forms circuits to process sensory information and to produce behavior. These circuits are most likely to be modified to form memories, just as we saw in the Martin study discussed earlier.

CREATING NOVEL CIRCUITS

Prior to the mid-1990s, it was generally assumed that the mammalian brain did not make new neurons in adulthood. The unexpected discovery in the 1970s that the brains of songbirds such as canaries grow new neurons to produce songs during the mating season led researchers to reconsider the possibility that the adult mammalian brain, too, might be capable of generating new neurons. This possibility can be tested directly by injecting animals with a compound that is taken up by cells when they divide to produce new cells, including neurons. When such a compound, bromodeoxyuridine (BrdU), is injected into adult rats, dividing cells incorporate it into their DNA. During later analysis, a specific stain can be used to identify the new neurons. Figure 13-19 shows such an analysis in the olfactory bulb and hippocampus.

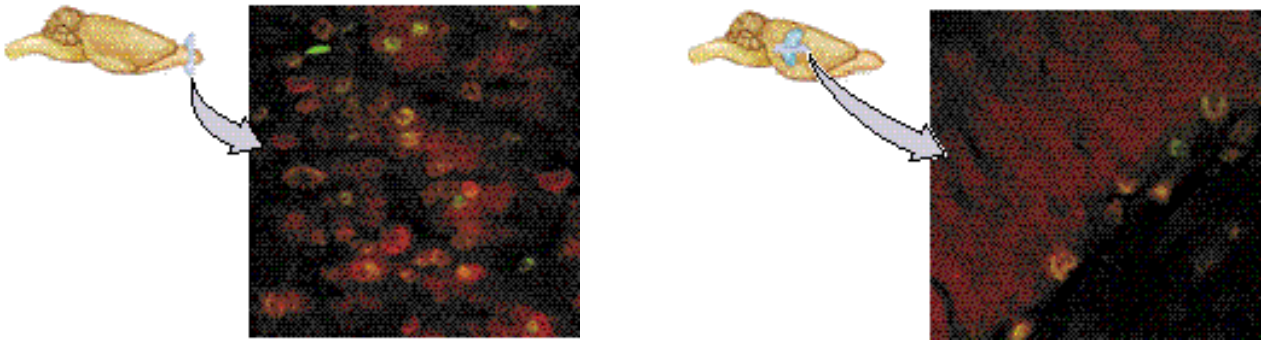


Figure 13-19

Confocal microscope photographs: cells stained red with an antibody to neurons called NeuN are neurons; cells stained green with an antibody to bromodeoxyuridine (BrdU) are new cells; cells stained yellow are positive for both red and green and are new neurons. *(Left)* Olfactory bulb. *(Right)* Hippocampus.

This technique has now yielded considerable evidence that the mammalian brain, including the primate brain,can generate neurons destined for the olfactory bulb, hippocampal formation,and even the neocortex of the frontal and temporal lobes (Eriksson et al., 1998; Gould et al., 1999). The reason for this generation is not yet clear; it may function to enhance brain plasticity, particularly with respect to processes underlying learning and memory. For example, Elizabeth Gould and her colleagues (1999) showed that the generation of new neurons in the hippocampus is enhanced when animals learn explicit memory tasks such as the Morris water task (see Figure 13-4). Furthermore,as we shall see,the generation of these new neurons appears to be increased by experience.

Enriched Experience and Plasticity

One way to stimulate the brain is to house animals in environments that provide some form of generalized sensory or motor experience. We described such an experiment in Chapter 7: Donald Hebb took laboratory rats home and let them have the run of his kitchen. After an interval, Hebb compared the enriched rats with a second group of rats that had remained in cages in his laboratory at McGill University, training both groups to solve various mazes. When the enriched animals performed better, Hebb concluded that one effect of the enriched experience was to enhance later learning. This important conclusion laid the foundation for the initiation of Head Start in the United States, a program to provide academic experiences for disadvantaged preschool-aged children.

Enriched rat enclosure

When subsequent investigators have worked with rats, they have opted for a more constrained enrichment procedure that uses some type of "enriched enclosure." For example, in our own studies, we place groups of six rats in enclosures. These enclosures give animals a rich social experience as well as extensive sensory and motor experience.

The most obvious consequence of such experience is an increase in brain weight that may be on the order of 10 percent relative to cage-reared animals, even though the enriched rats typically weigh less, in part because they get more exercise. The key question is, What is responsible for the increased brain weight? A comprehensive series of studies by Anita Sirevaag and Bill Greenough (1988) used light- and electron-microscopic techniques to analyze 36 different aspects of cortical synaptic, cellular, and vascular morphology in rats raised either in cages or in complex environments. The simple conclusion was that there is a coordinated change not only in the extent of dendrites but also in glial, vascular, and metabolic processes in response to differential experiences (see Figure 13-20). Animals with enriched experience have not only more

synapses per neuron but also more astrocytic material, more blood capillaries, and higher mitochondrial volume. (Higher mitochondrial volume means greater metabolic activity.) It is therefore clear that when the brain changes in response to experience,the expected neural changes occur, but there are also adjustments in the metabolic requirements of the larger neurons.

Gerd Kempermann and his colleagues (1998) sought to determine whether experience altered the number of neurons in the brain. To test this idea, they compared the generation of neurons in the hippocampus of mice housed in complex environments with that of mice reared in laboratory cages. They located the number of new neurons by injecting the animals with BrdU several times in the course of their complex housing experience. The BrdU was incorporated into new neurons that were generated in the brain during the experiment. When they later looked at the hippocampus, they found more new neurons in the complex-housed rats than in the cage-housed rats. Although the investigators did not look in other parts of the brain, such as the olfactory bulb, it is reasonable to expect that similar changes may have taken place in other structures. This result is exciting because it implies that experience not only can alter existing circuitry but also can influence the generation of new neurons,and thus new circuitry.

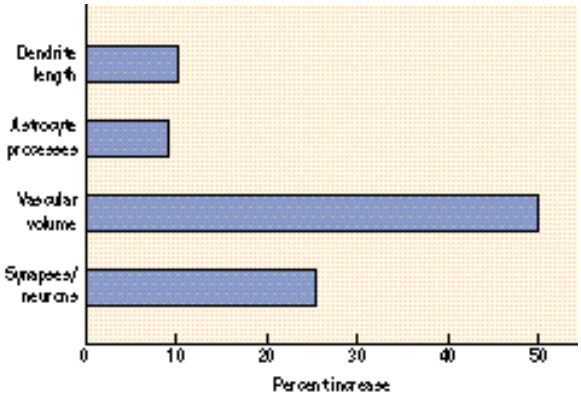


Figure 13-20

A schematic summary of some of the changes that take place in the cortex in response to experience. Note that such changes are found not only in neurons but also in astrocytes and vasculature.

Based on data from "Differential Rearing Effects on Rat Visual Cortex Synapses. I. Synaptic and Neuronal Density and Synapses per Neuron," by A. Turner & W. T. Greenough, *Brain Research,* 1985, *329,* 195–203; "Differential Rearing Effects on Rat Visual Cortex Synapses. III. Neuronal and Glial Nuclei," by A. M. Sirevaag and W. T. Greenough, *Brain Research,* 1987, *424,* 320–332; and "Experience-Dependent Changes in Dendritic Arbor and Spine Density in Neocortex Vary with Age and Sex," by R. Gibb, G. Garny, and B. Kolb, *Neurobiology of Learning and Memory,* 2001.

Sensory or Motor Training and Plasticity

The studies showing neuronal change in animals housed in complex environments demonstrate that large areas of the brain can be changed with such experience. This finding leads us to ask whether specific experiences would produce synaptic changes in localized cerebral regions.One way to approach this question is to give animals specific experiences and then to see how their brains have been changed by the experiences. Another way is to look at the brains of people who have had a lifetime of some particular experience. We will consider each of these research strategies separately.

MANIPULATING EXPERIENCE EXPERIMENTALLY

Perhaps the most convincing study of this sort was done by Fen-Lei Chang and Bill Greenough (1982). They took advantage of the fact that the visual pathways of the laboratory rat are about 90 percent crossed. That is, about 90 percent of the connections from the left eye to the cortex project via the right lateral geniculate nucleus to the right hemisphere, and vice versa for the right eye. Chang and Greenough placed a patch over one eye of each rat and then trained the animals in a maze. The visual cortex of only one eye would receive input about the maze, but the auditory, olfactory, tactile, and motor regions of both hemispheres would be equally active as the animals explored the maze. (Chang and Greenough also severed the corpus callosum so that the two hemispheres could not communicate and share information about the world.) Comparison of the neurons in the two hemispheres revealed that those in the visual cortex of the trained hemisphere had more extensive dendrites. The researchers concluded that some feature associated with the reception, processing, or storage of visual input from training was responsible for the formation of new synapses because the hemispheres did not differ in other respects.

Complementary studies have been conducted in monkeys by Randy Nudo and his colleagues. In the discussions of both the sensory and motor systems (Chapters 8–10), you learned that the sensory and motor worlds are represented by cortical maps. For example, in the motor system there are maps of the body that represent discrete muscles and movements (see Figure 10-17). In the course of mapping the motor cortex of

monkeys, Nudo and his colleagues (1997) noted striking individual differences in the topography of the maps. They speculated that the individual map variability might reflect each animal's experiences up to the time in life at which the cortical map was derived. To test this idea directly, they trained one group of monkeys to retrieve food pellets from a small food well while another group retrieved them from a substantially larger well, as illustrated in Figure 13-21. Monkeys in the two groups were matched for number of finger flexions, which totaled about 12,000 for the entire study. No systematic changes were seen in motor hand maps in the monkeys retrieving food pellets from the large well, but those animals retrieving pellets from the small well showed robust changes that were presumably due to the more demanding motor requirements of the small-well condition.

Most studies demonstrating plasticity in the motor cortex have been performed on laboratory animals in which the cortex has been mapped by microelectrode stimulation. Now the development of new imaging techniques, such as transmagnetic stimulation and functional magnetic resonance imaging (fMRI), has made it possible to show parallel results in humans who have special motor skills. For example, there is an increased cortical representation of the fingers of the left hand in musicians who play string instruments and an increased cortical representation of the reading finger in Braille readers. Thus, the functional organization of the motor cortex is altered by skilled use in humans. It can also be altered by chronic injury. Jon Kaas (2000) showed that when the sensory nerves from one limb are severed in monkeys, large-scale changes in the somatosensory maps ensue. In particular, in the absence of input, the relevant part of the cortex no longer responds to stimulation of the limb, which is not surprising. But this cortex does not remain inactive. Rather, the denervated cortex begins to respond to input from other parts of the body. The region that once would have responded to the hand now responds to stimulation on the

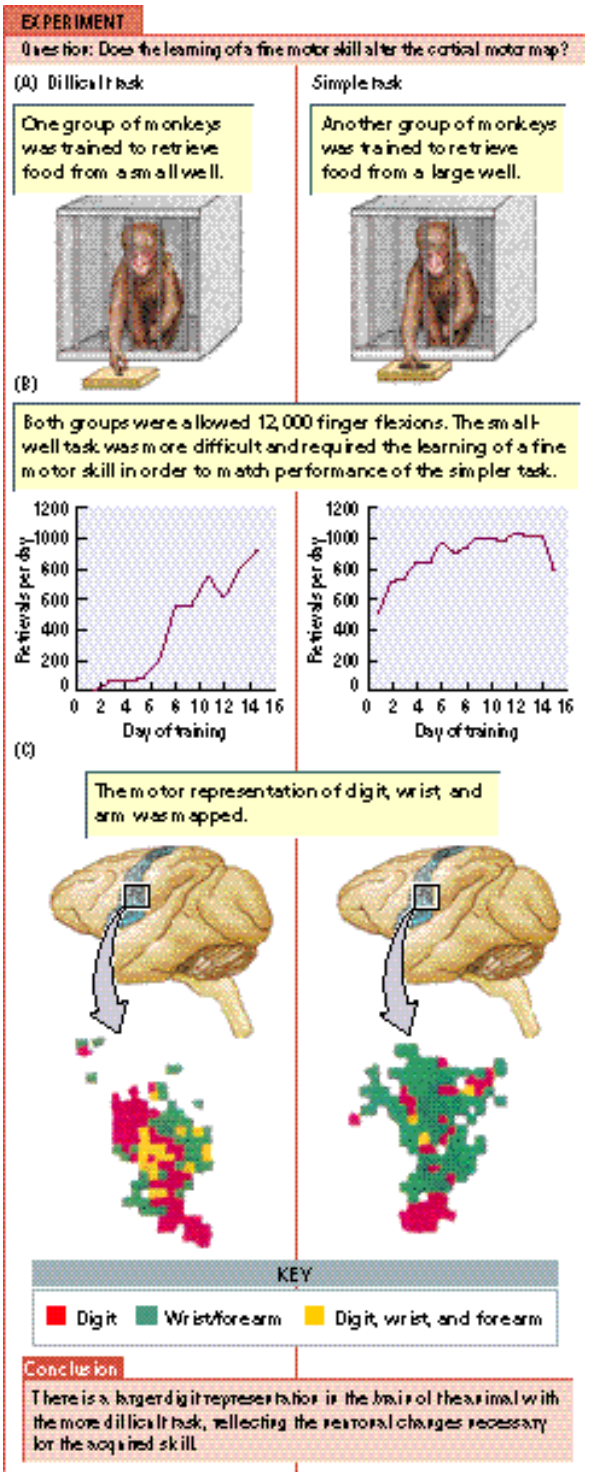


Figure 13-21

Differential effects of motor-skill acquisition and motor use on functional organization of the squirrel monkey motor cortex. **(A)** Training procedures consisted of retrieving small banana-flavored pellets from either a small or large well. The monkey is able to insert the entire hand into the large well but can insert only one or two fingers into the smaller well. **(B)** The monkeys trained on the small well improved with practice (making fewer finger flexions per food retrieval) over the course of training. In order to control for mere motor activity, the researchers trained both groups until they made 12,000 finger flexions. **(C)** Maps of forelimb movements were produced by microelectrode stimulation of the cortex. The maps showed systematic changes in the animals trained with the small, but not the large, well. This experiment demonstrated that the functional topography of the motor cortex is shaped by learning new motor skills, not simply by repetitive motor use.

Adapted from "Adaptive Plasticity in Primate Motor Cortex as a Consequence of Behavioral Experience and Neuronal Injury," by R.J. Nudo, E.J. Plautz, and G.W. Milliken, *Seminars in Neuroscience*, 1997, *9*, p. 20.

face, whose area is normally adjacent to the hand area. Similar results can be found in the cortical maps of people who have had limbs amputated. For example, Vilayanur Ramachandran (1993) found that when the face of a limb amputee is brushed lightly with a cotton swab, there is a sensation of the amputated hand being touched. Figure 13-22 illustrates the rough map of the hand that Ramachandran was actually able to chart on the face. The likely explanation is that the face area has expanded to occupy the denervated limb cortex, but the brain has circuits that still "believe" that the activity of this cortex represents input from the limb. This may explain the "phantom limb" pain often experienced by amputees.

The idea that experience can alter cortical maps can be demonstrated with other types of experience. For example, if animals are trained to make certain digit movements over and over again, the cortical representation of those digits expands at the expense of the remaining areas. Similarly, if animals are trained extensively to discriminate among different sensory stimuli such as tones, the cortical areas responding to those stimuli are increased in size. We can speculate that one of the effects of musical training is to alter the motor representations of the digits used to play different instruments or to alter the auditory representations of specific sound frequencies. This is essentially a form of memory, and the underlying synaptic changes are likely to occur on the appropriate sensory or motor cortical maps.

EXPERIENCE-DEPENDENT CHANGE IN THE HUMAN BRAIN

We saw from the Ramachandran amputee study that the human brain appears to change with altered experience. This study did not directly examine neuronal change, however; neuronal change was inferred from behavior. The only way to directly examine synaptic change is to look directly at brain tissue. It is obviously not practical to manipulate experiences experimentally in people and then examine their brains. It is possible to examine the brains of people who died from nonneurological causes and then to relate the structure of their cortical neurons to their experience.

One way to test this idea is to look for a relationship between neuronal structure and education. Arnold Scheibel and his colleagues conducted many such studies in the past decade (Jacobs & Scheibel, 1993; Jacobs, Scholl, & Scheibel, 1993). In one study, they found a relationship between the size of the dendrites in a cortical language area (Wernicke's area) and the amount of education. The cortical neurons from the brains of deceased people with a college education had more dendritic branches than did those from people with a high school education, which, in turn, had more dendritic material than did those from people with less than a high school education. Of course, it may be that people who have larger dendrites in their neurons are more likely to go to college, but that possibility is not easy to test.

Another way to look at the relationship between human brain structure and behavior is to correlate the functional abilities of people with neuronal structure. For example, one might expect to find differences in language-related areas between people with high and low verbal abilities. This experiment is difficult to do, however, because it presupposes behavioral measures taken prior to death, and such measures are not normally available. However, Scheibel and his colleagues took advantage of the now well-documented observation that, on average, females have superior verbal abilities to males. When they examined the structure of neurons in Wernicke's area, they found that females have more extensive dendritic branching than males do. Furthermore, in a subsequent study, they found that this sex difference was present as early as age nine, suggesting that such sex differences emerge within the first decade. In fact, it is known that young girls do tend to have significantly better verbal skills than young boys do.

Finally, these investigators approached the link between experience and neuronal morphology in a slightly different way. They began with two hypotheses. First, they suggested that there is a relationship between the complexity of dendritic branching

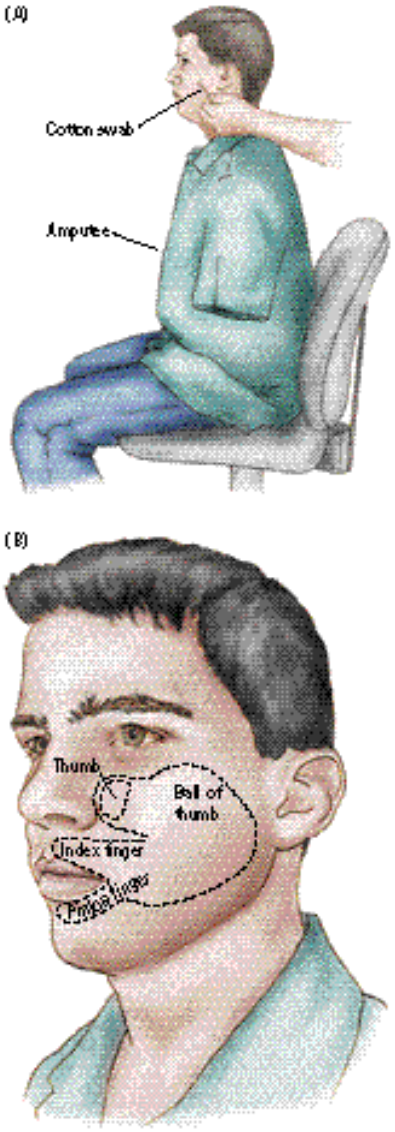


Figure 13-22

When the face of an amputee is stroked lightly with a cotton swab **(A)**, there is an experience of the missing hand being lightly touched. **(B)** This hand experience forms a representation on the face. As in the normal map of the somatosensory cortex, the thumb is disproportionately large.

Adapted from "Behavioral and Magnetoencephalographic Correlates of Plasticity in the Adult Human Brain," by V.S. Ramachandran, 1993, *Proceedings of the National Academy of Sciences, USA, 90.*

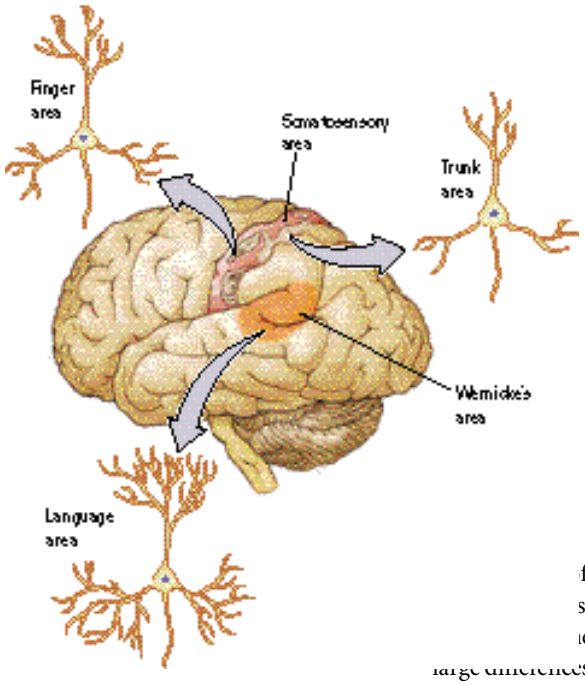


Figure 13-23

An illustration of Scheibel's hypothesis that cell complexity is related to the computational demands required for the cell. Cells that represent the trunk area of the body have relatively less computational demand than that required for cells representing the finger region. In turn, cells engaged in more cognitive functions (such as language, as in Wernicke's area) would have greater computational demands than those engaged in finger functions.

and the nature of the computational tasks performed by a brain area. To test this hypothesis, they examined the dendritic structure of neurons in different cortical regions that involved different computational tasks. For example, when they compared the structure of neurons corresponding to the somatosensory representation of the trunk with those for the fingers, they found the latter to have more complex cells. They reasoned that the somatosensory inputs from receptive fields on the chest wall would constitute less of a computational challenge to cortical neurons than would those from the fingers and that the neurons representing the chest would therefore be less complex. This hypothesis was shown to be correct (see Figure 13-23). Similarly, when they compared the cells in the finger area with those in the supramarginal gyrus (SMG), a region of the parietal lobe that is associated with higher cognitive processes (that is, thinking), they found the SMG neurons to be more complex.

The second hypothesis was that dendritic branching in all regions is subject to experience-dependent change. As a result, they hypothesized that predominant life experience (for example, occupation) should alter f dendrites. Although they did not test this hypothesis directly, they did sting observation. In their study comparing cells in the trunk area, the fin- e SMG, they found curious individual differences. For example,especially large differences in trunk and finger neurons were found in the brains of people who had a high level of finger dexterity maintained over long periods of time (for example, typists). In contrast, no difference between trunk and finger was found in a sales representative. One would not expect a good deal of specialized finger use in this occupation, which would mean less complex demands on the finger neurons.

In summary, although the studies showing a relationship between experience and neural structure in humans are correlative studies, rather than actual experiments, their findings are consistent with those observed in studies of other species. We are thus led to the general conclusion that specific experiences can produce localized changes in the synaptic organization of the brain. It seems likely that such changes form the structural basis of memory.

Plasticity, Hormones, Trophic Factors, and Drugs

Articles in newspapers and popular magazines often report that drugs can damage your brain. Some drugs certainly do act as toxins and can selectively kill brain regions, but a more realistic mode of action of drugs is to *change* the brain. Although not many studies have looked at drug-induced morphological changes, there is evidence that some compounds can profoundly change the synaptic organization of the brain. These compounds include hormones, neurotrophic factors, and psychoactive drugs. We will briefly consider each of these kinds of substances.

HORMONES

We have seen in earlier chapters that the levels of circulating hormones play a critical role both in determining the structure of the brain and in eliciting certain behaviors in adulthood. Although it was once believed that the structural effects of hormones were expressed only during development, it is now generally agreed that even adult neurons can respond to hormonal manipulations with dramatic structural changes. We will consider the actions of two types of hormones, the gonadal hormones and the glucocorticoids, which are stress-related hormones.

We encountered the gonadal hormones in Chapters 7 and 11. Research has established that there are differences in the structure of neurons in the cortices of male versus

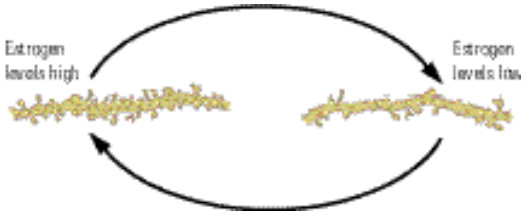


Figure 13-24

Sections of dendrites from times of high and low levels of estrogen during the rat's 4-day estrous cycle. There are many more dendritic spines during the period of high estrogen.

Adapted from "Naturally Occurring Fluctuation in Dendritic Spine Density on Adult Hippocampal Pyramidal Neurons," by C.S. Woolley, E. Gould, M. Frankfurt, and B.S. McEwen, 1990, *Journal of Neuroscience, 10,* p. 4038.

female rats and that these differences depend on gonadal hormones. What is more surprising, perhaps, is that gonadal hormones continue to influence cell structure and behavior in adulthood. Elizabeth Hampson and Doreen Kimura (1988) showed that the performance of women on various cognitive tasks changes throughout the menstrual cycle as the estrogen level goes up and down. This fluctuation in estrogen level appears to alter the structure of neurons and astrocytes in the neocortex and hippocampus, which likely accounts for at least part of the behavioral fluctuation. Figure 13-24 illustrates changes in the dendritic spines of female rats at different phases of their 4-day estrous cycle. As the estrogen level rises, the number of synapses rises; as the estrogen level drops, the number of synapses declines. Curiously, the influence of estrogen on cell structure may be different in the hippocampus and neocortex. Jane Stewart has found, for example, that when the ovaries of middle-aged female rats are removed, estrogen levels drop sharply, producing an increase in the number of spines on pyramidal cells throughout the neocortex but a decrease in spine density in the hippocampus (Stewart & Kolb, 1994). It is not immediately obvious how these synaptic changes might influence processes such as memory, but it is a reasonable question—especially because menopausal women also experience sharp drops in estrogen levels and a corresponding decline in verbal memory ability. This question is also relevant to middle-aged men, who show a slow decline in testosterone levels that is correlated with a drop in spatial ability. Rats that are gonadectomized in adulthood show an increase in cortical spine density, much like the ovariectomized females, although we do not know how this change is related to spatial behavior. Nonetheless, it is reasonable to suppose that testosterone levels might influence spatial memory.

When the body is stressed,the pituitary gland produces adrenocorticotrophic hormone (ACTH), which stimulates the adrenal cortex to produce hormones known as **glucocorticoids.** Glucocorticoids have many actions on the body, including the brain. Robert Sapolsky (1992) proposed that glucocorticoids can sometimes be neurotoxic. In particular, he has found that with prolonged stress, cells in the hippocampus appear to be killed by glucocorticoids.Elizabeth Gould and her colleagues (1998) showed that even relatively brief periods of stress can reduce the number of new granule cells produced in the hippocampus in monkeys, presumably through the actions of stress-related hormones. Evidence of neuron death and reduced neuron generation in the hippocampus has obvious implications for the behavior of animals, especially for processes like memory.

In sum, hormones can alter the synaptic organization of the brain and even the number of neurons in the brain. Little is known today about the behavioral consequences of such changes, but it is likely that hormones can alter the course of plastic changes in the brain.

NEUROTROPHIC FACTORS

Neurotrophic factors are a group of compounds that act to reorganize neural circuits. These compounds are listed in Table 13-2. The first neurotrophic factor was discovered in the peripheral nervous system more than 30 years ago; it is known as **nerve growth factor (NGF).** NGF is trophic (that is, having to do with the process of nutrition) in

Glucocorticoid. One of a group of hormones, secreted in times of stress, that are important in protein and carbohydrate metabolism.

Neurotrophic factors. A group of compounds that act to promote the growth and survival of neurons.

Table 13-2 Molecules Exhibiting Neurotrophic Activities

Proteins initially characterized as neurotrophic factors
Nerve growth factor (NGF)
Brain-derived neurotrophic factor (BDNF)
Neurotrophin-3 (NT-3)
Ciliary neurotrophic factor (CNTF)
Growth factors with neurotrophic activity
Fibroblast growth factor, acidic (aFGF or FGF-1)
Fibroblast growth factor, basic (bFGF or FGF-2)
Epidermal growth factor (EGF)
Insulin-like growth factor (ILGF)
Transforming growth factor (TGF)
Lymphokines (interleukin 1, 3, 6 or IL-1, IL-3, IL-6)
Protease nexin I, II
Cholinergic neuronal differentiation factor

the sense that it stimulates neurons to grow dendrites and synapses, and in some cases it promotes the survival of neurons. Trophic factors are produced in the brain, by both neurons and glia. Trophic factors can affect neurons both through cell-membrane receptors and by actually entering the neuron to act internally on its operation. For example, trophic factors may be released postsynaptically to act as signals that can influence the presynaptic cell. Recall from Chapter 5 that the Hebb synapse is hypothesized to have just such a mechanism.

Experience stimulates the production of trophic factors, so neurotrophic factors have been proposed as agents of synaptic change. For example, brain-derived neurotrophic factor (BDNF) is increased when animals solve specific problems such as mazes. This finding has led to speculation that the release of BDNF may enhance plastic changes, such as the growth of dendrites and synapses. Unfortunately, although many researchers would like to conclude that BDNF has a role in learning, this conclusion does not necessarily follow. The behavior of animals when they solve mazes is different from their behavior when they remain in cages, so we must first demonstrate that changes in BDNF, NGF, or any other trophic factor are actually related to the formation of new synapses. Nevertheless, if we assume that trophic factors do act as agents of synaptic change, then we should be able to use the presence of increased trophic factor activity during learning as a marker of where to look for changed synapses associated with learning and memory.

PSYCHOACTIVE DRUGS

Many people commonly take stimulant drugs like caffeine, and some use more psychoactively stimulating drugs like nicotine, amphetamine, or cocaine. The long-term consequences of abusing psychoactive drugs are now well documented, but the question of why the drugs cause these problems remains to be solved. One explanation for the behavioral changes associated with chronic psychoactive drug abuse is that the brain is changed by the drugs. One experimental demonstration of these changes is known as **drug-induced behavioral sensitization,** often referred to as just *behavioral sensitization*. Behavioral sensitization is the progressive increase in the behavioral actions of a drug that occur after repeated administration of that drug, even when the amount given in each dose does not change. Behavioral sensitization occurs with most psychoactive drugs, including amphetamine, cocaine, morphine, and nicotine. In Chapter 5, we saw that *Aplysia* became more sensitive to a stimulus after repeated ex-

Drug-induced behavioral sensitization. The phenomenon whereby there is an escalating behavioral response to repeated administration of a psychomotor stimulant such as amphetamine, cocaine, or nicotine.

posure to it. Psychoactive drugs appear to have a parallel action: they lead to increased behavioral sensitivity to their actions. For example,a rat given a small dose of amphetamine may show an increase in activity. When the rat is given the same dose of amphetamine on subsequent occasions, the increase in activity is progressively larger. If no drug is given for weeks or even months,and then the drug is given in the same dose as before, behavioral sensitization continues to occur, which means that some type of long-lasting change must occur in the brain in response to the drug. Behavioral sensitization can therefore be viewed as a form of memory for a particular drug.

The parallel between drug-induced behavioral sensitization and other forms of memory leads us to ask if the changes in the brain after behavioral sensitization are similar to those found after other forms of learning. They are. For example,there is evidence of increased numbers of receptors at synapses and of more synapses in sensitized animals. In a series of studies, Terry Robinson and his colleagues have found a dramatic increase in dendritic growth and spine density in rats that were sensitized to amphetamine or cocaine relative to rats that received injections of a saline solution (Robinson & Kolb, 1999). Figure 13-25 compares the effects of amphetamine and saline treatments on cells in the nucleus accumbens. It can be seen that neurons in the amphetamine-treated brains have more dendritic branches and increased spine density. These plastic changes were not found throughout the brain, however. Rather, they were localized to such regions as the prefrontal cortex and nucleus accumbens, both of which receive a large dopamine projection. Recall from Chapters 6 and 11 that dopamine is believed to play a significant role in the rewarding properties of drugs.

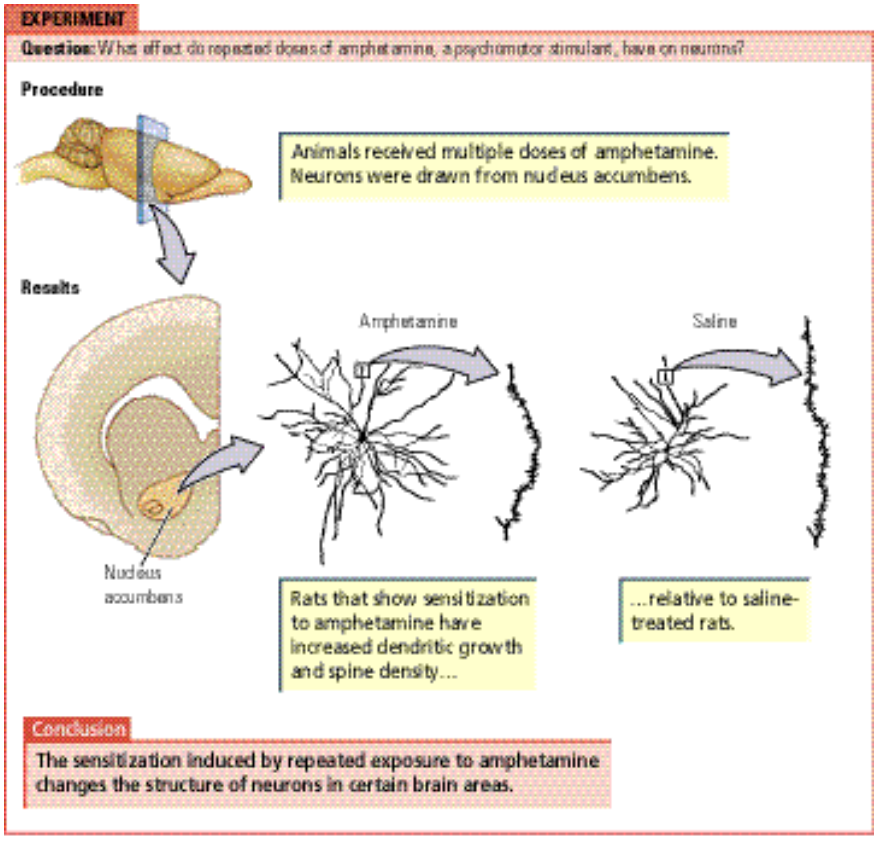


Figure 13-25

Neurons in the nucleus accumbens of saline- and amphetamine-treated rats. Rats that show sensitization to amphetamine (or cocaine) experience increased dendritic growth and increased spine density relative to saline-treated rats. Repeated exposure to psychoactive stimulant drugs thus alters the structure of cells in the brain.

Adapted from "Persistent Structural Adaptations in Nucleus Accumbens and Prefrontal Cortex Neurons Produced by Prior Experience with Amphetamine," by T.E. Robinson and B. Kolb, 1997, *Journal of Neuroscience, 17,* p. 8495.

In Review

We have seen that experience produces plastic changes in the brain, including the growth of dendrites, the formation of synapses, and the production of new neurons. Further, like environmental stimulation, it appears that hormones, neurotrophic factors, and psychoactive drugs can produce long-lasting effects on brain morphology that are strikingly similar to those observed when animals show evidence of memory for sensory events. These changes in morphology include not only changes in synaptic organization, as inferred from the dendritic analyses, but also changes in the neuron numbers, at least in the hippocampus. Thus, the neural changes that correlate with memory are similar to those observed in other situations of behavioral change.

We can infer that the nervous system appears to be conservative in its use of mechanisms related to behavioral change. This is an important message, because it implies that if we wish to change the brain, as after injury or disease, then we should look for treatments that will produce the types of neural changes that we have found to be related to memory and other forms of behavioral change. Recall that Donna showed significant recovery from her head injury; it is reasonable to ask whether that recovery was related to neuronal change. This question is the next, and last, one to be considered in this chapter.

RECOVERY FROM BRAIN INJURY

In this chapter's introductory story, Donna showed some, albeit incomplete, recovery of function after a brain injury. Partial recovery of function is common after brain injury, and the average person would probably say that the process of recovery requires that the injured person relearn lost skills, whether walking, talking, or use of the fingers. But what exactly does recovery entail? After all, a person with a brain injury or brain disease has lost neurons, so the brain may be missing critical structures that are needed for learning. Recall, for example, that H.M. has shown no recovery of his lost memory capacities, even after 50 years of practice in trying to remember information. The requisite neuron structures are no longer there, so relearning is simply not possible. In H.M.'s case, the only solution would be to replace his lost medial temporal structures,a procedure that at present is not feasible. But other people, such as Donna, do show some recovery. On the basis of what we have described in this chapter, we can identify three different ways in which Donna could recover from brain injury: she could learn new ways to solve problems, she could reorganize the brain to do more with less, and she could generate new neurons to produce new neural circuits. We will briefly examine these three possibilities.

The Three-Legged Cat Solution

The simplest solution to recovery from brain injury is to compensate for the injury in a manner that we call the "three-legged cat solution." Consider cats that lose a leg to accident (and subsequent veterinary treatment). These cats quickly learn to compensate for the missing limb and once again become mobile; they can be regarded as having shown recovery of function. The limb is still gone, of course, but the behavior has changed in compensation. A similar explanation can account for many instances of apparent recovery of function after brain injury. Imagine a right-handed person who has a stroke that leads to loss of use of the right hand and arm. Unable to write with the

affected limb, she switches to her left hand. This type of behavioral compensation is presumably associated with some sort of change in the brain. After all, if a person learns to use the opposite hand to write,some changes in the nervous system must underlie this new skill.

The New-Circuit Solution

A second way to recover from brain damage is for the brain to change its neural connections to overcome the neural loss. This is most easily accomplished by processes that are similar to those we considered for other forms of plasticity. That is, the brain forms new connections that allow it to "do more with less." Although this would seem to be a logical change in the brain, such changes appear to be fairly small. As a result, there is relatively modest recovery in most instances of brain injury, *unless there is some form of intervention*. Stated differently, recovery from brain damage can be increased significantly if the individual engages in some form of behavioral or pharmacological therapy. Thus, the therapy must play a role in stimulating the brain to make new connections and to do more with less.

Behavioral therapy, such as speech therapy or physiotherapy, presumably increases brain activity, which facilitates the neural changes. In a pharmacological intervention, the patient takes a drug that is known to influence brain plasticity. An example is NGF. When NGF is given to animals with strokes that damaged the motor cortex, there is an improvement in motor functions, such as reaching with the forelimb to obtain food (Figure 13-26). The behavioral changes are correlated with a dramatic increase in dendritic branching and spine density in the remaining, intact motor regions. The morphological changes are correlated with improved motor functions, such as reaching with the forelimb to obtain food, as illustrated in Figure 13-21 (Kolb et al., 1997). Recovery is by no means complete, but this is not surprising because brain tissue is still missing.

In principle, we might expect that any drug that stimulates the growth of new connections would help people recover from brain injury. There is one important constraint, however. The neural growth must be in regions of the brain that could influence a particular lost function. For example, if a drug stimulated growth of synapses on cells in the visual cortex, we would not expect to find enhanced recovery of hand use. The visual neurons play no direct role in moving the hand. Rather, we would need a drug that stimulated the growth of synapses on neurons that could control hand use, such as neurons in the premotor or prefrontal cortex. We saw earlier that amphetamine has this action, so we might predict that amphetamine would stimulate motor recovery. This possibility is now undergoing clinical trials.

Bryan Kolb

The Lost-Neuron-Replacement Solution

The idea that brain tissue could be transplanted from one animal to another goes back to the beginning of the twentieth century. There is now good evidence that tissue from embryonic brains can be transplanted and will grow and form some connections in the new brain. Unfortunately, in contrast to transplanted hearts or livers, transplanted brain tissue functions poorly. The procedure seems most suited to conditions in which a small number of functional cells are required, such as in the replacement of dopamine-producing cells in Parkinson's disease. In fact, dopamine-producing cells have been surgically transplanted into the striatum of at least 50 Parkinson patients to date. Although the disease has not been reversed,some patients,especially the younger ones,have shown functional gains that justify the procedure. Nonetheless,the fact that the embryonic tissue is taken from human fetuses raises serious ethical issues that will not be easily resolved.

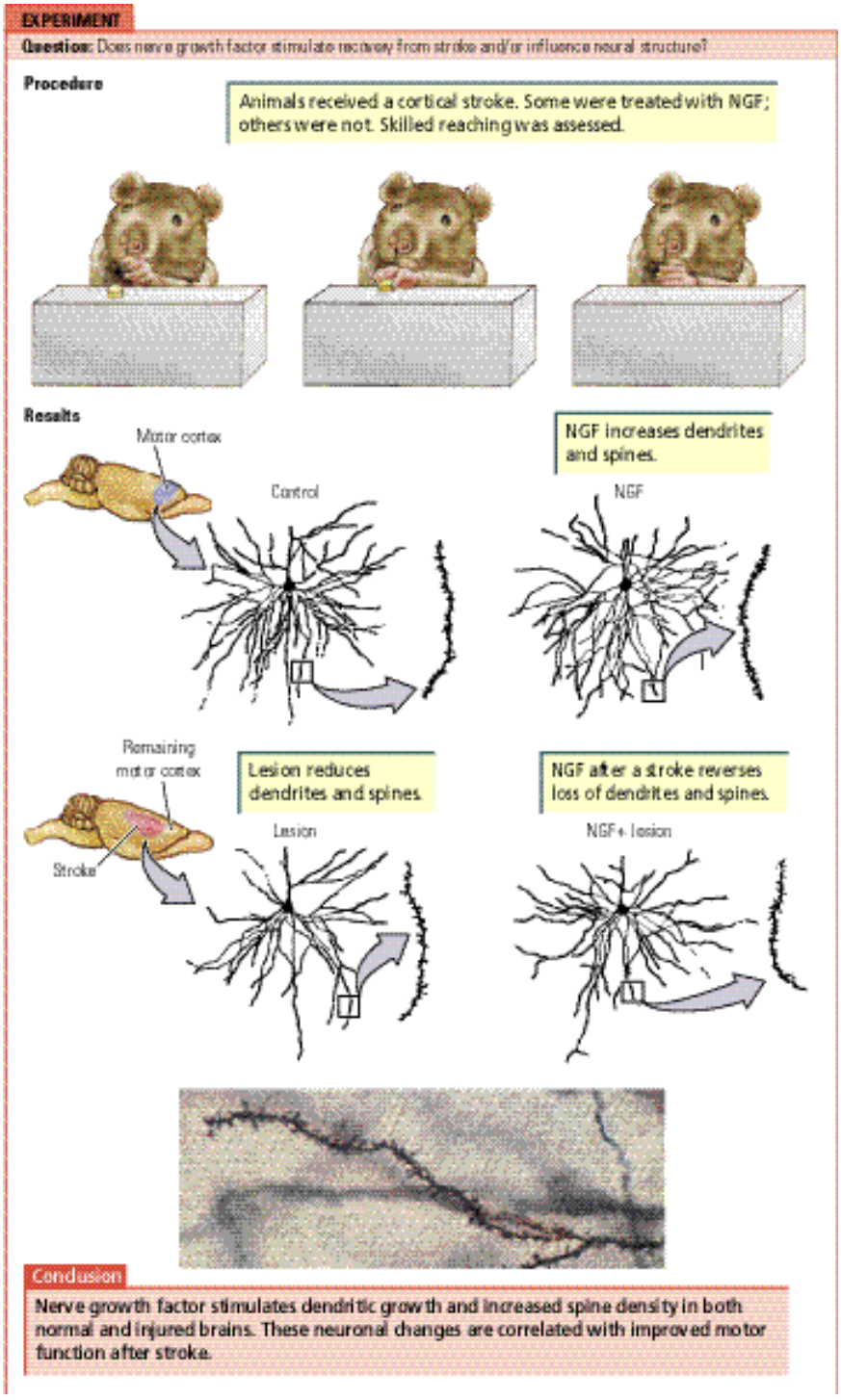


Figure 13-26

In the reaching task shown, rats must make skilled forelimb movements to obtain a food reward. Rats treated with NGF after motor-cortex injury show better performance on this task than do rats that receive no treatment. The cells from the NGF-treated rats show a marked increase in both dendritic branching and spine density. This plastic change is hypothesized to be responsible for the partial functional recovery in the rats treated with NGF.

Adapted from "Nerve Growth Factor Treatment Prevents Dendritic Atrophy and Promotes Recovery of Function After Cortical Injury," by B. Kolb, S. Cote, A. Ribeiro-da-Silva, and A.C. Cuello, 1997, *Neuroscience*, *76,* p. 1146.

There is a second way to replace lost neurons. We saw earlier that experience can induce the brain to generate new neurons, so we know that the brain is capable of making neurons in adulthood. The challenge is to get the brain to do it after an injury. The first breakthrough in this research was made by Brent Reynolds and Sam Weiss

(1992). Cells lining the ventricle of adult mice were removed and placed in a culture medium. The researchers demonstrated that if the right trophic factors are added, the cells begin to divide and can produce new neurons and glia. Furthermore, if the trophic factors—particularly **epidermal growth factor** (EGF)—are infused into the ventricle of a living animal, the subventricular zone generates cells that migrate into the striatum and eventually differentiate into neurons and glia.

In principle, it ought to be possible to use trophic factors to stimulate the subventricular zone to generate new cells in the injured brain. If these new cells were to migrate to the site of injury and essentially to regenerate the lost area, then it might be possible to restore at least some of the lost functions. It seems unlikely that all lost behaviors could be restored, however, because the new neurons would have to establish the same connections with the rest of the brain that the lost neurons once had. This would be a daunting task, because the connections would have to be formed in an adult brain that already had billions of connections. Nonetheless, there is at least reason to hope that such a treatment might someday be feasible.

There may be another way to use trophic factors to stimulate neurogenesis and enhance recovery. Recall that regions such as the hippocampus and olfactory bulb normally produce new neurons in adulthood and that the number of neurons in these areas can be influenced by experience. It is possible, therefore, that we could stimulate the generation of new neurons in intact regions of the injured brains and that these neurons could help the brain develop new circuits to restore partial functioning. Thus, experience and trophic factors are likely to be used in studies of recovery from brain injury in the coming years.

In Review

Learning to recover from brain injury poses a special problem, because the brain may lose large areas of neurons and their associated functions. There are three ways to compensate for the loss of neurons: learn new ways to solve problems, reorganize the brain to do more with less, and replace the lost neurons. Although complete recovery is not currently practical, it is possible to use all three strategies to enhance recovery from injury. Moreover, it is likely that rehabilitation programs will begin to look at the possibility of combining these three ways to further enhance recovery. In each case, however, recovery entails taking advantage of the brain's capacity to change.

SUMMARY

Donna's experience with brain injury illustrates the brain's ability to change its structure and function throughout a lifetime. The discussion leads to the following questions.

1. *How does the brain learn and remember?* There are two distinctly different forms of learning and memory, which may be referred to as implicit and explicit memory. The neural circuits underlying these forms of memory are distinctly different: the system for explicit memory involves medial temporal structures; the system for implicit memory includes the basal ganglia. There are multiple subsystems within the explicit and implicit systems, with different ones controlling different forms of memory. A third form of memory is emotional memory, which has characteristics of both implicit and explicit memory. The neural circuits for emotional memory are unique in that they include the amygdala.

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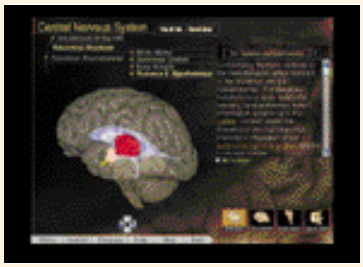

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2. *What changes take place in the brain in response to experience?* The brain has the capacity for structural change, which is presumed to underlie functional change. The brain changes in two fundamental ways. First, changes occur in existing neural circuits. Second, novel neural circuits are formed, both by forming new connections among existing neurons and by generating new neurons.
3. *What stimulates plastic change in the brain?* The key to brain plasticity is neural activity. Through such activity, synapses are formed and changed. Neural activity can be induced by general or specific experience, as well as by electrical or chemical stimulation of the brain. Chemical stimulation may range from hormones to neurotrophic compounds to psychoactive drugs. Much of the brain is capable of plastic change with experience. Different experiences lead to changes in different neural systems.
4. *How might brain plasticity stimulate recovery from injury?* There are plastic changes after brain injury that parallel those seen when the brain changes with experience. Changes related to recovery do not always occur spontaneously, however, and must be stimulated either by behavioral training or by the stimulating effects of psychoactive drugs or neurotrophic factors. The key to stimulating recovery from brain injury is to produce an increase in the plastic changes underlying the recovery.

KEY TERMS

brain plasticity, p. 489
drug-induced behavioral sensitization, p. 520
explicit memory, p. 495
fear conditioning, p. 492
glucocorticoid, p. 519
implicit memory, p. 495
instrumental conditioning, p. 492
Korsakoff's syndrome, p. 506
learning, p. 490
learning set, p. 493
memory, p. 490
neurotrophic factors, p. 519
Pavlovian conditioning, p. 491

REVIEW QUESTIONS

1. How does experience change the brain?
2. What are the critical differences between the studies of learning conducted by Pavlov and those conducted by Thorndike?
3. Distinguish among explicit, implicit, and emotional memory; what are the circuits for each?
4. What is the structural basis of brain plasticity, and what are various methods for studying its relation to behavior?
5. Why do changes in sensory representations occur after amputation of a limb?
6. What mechanisms might account for recovery from brain injury?

FOR FURTHER THOUGHT

1. Imagine that a person has a stroke and loses a large portion of the left hemisphere, rendering him unable to speak. Imagine further that a treatment has been devised in which new neurons can be generated to replace the lost brain regions. What would be the behavioral consequences of this brain regeneration? Would the person be the same as he was before the stroke? (Hint: The new cells would have no experiences.)
2. How do we learn from experience?

RECOMMENDED READING

Florence,S.L., Jain,N.,& Kaas, J.H.(1997).Plasticity of somatosensory cortex in primates. *Seminars in Neuroscience,9,* 3–12. Jon Kaas and his colleagues are leaders in the study of brain plasticity. This very readable review introduces the reader to the exciting discoveries that Kaas and his colleagues are making in the study of cortical plasticity in monkeys.

Fuster, J.M.(1995). *Memory in the cerebral cortex.* Cambridge,MA:MIT Press. Joaquin Fuster has summarized the evidence on how the cortex codes information for storage and retrieval,and he presents a cogent theory of how the cortex allows us to learn and to remember.

Gazzaniga,M.S.(Ed.).(2000). *The new cognitive neurosciences*. Cambridge,MA:MIT Press. This edited book spans the entire field of cognitive neuroscience. There is something for everyone in this broad and well-written collection of chapters.

Hebb, D. O. (1949). *The organization of behavior*. New York: Wiley. Although this book was written 50 years ago, it remains the clearest introduction to the fundamental questions about how the brain can learn.

Kolb, B., & Whishaw, I.Q.(1998). Brain plasticity and behavior. A*nnual Review of Psychology, 49,* 43–64. The authors provide a general review of the field of brain plasticity and behavior. Any student writing a paper on this topic would do well to start with this paper and its extensive bibliography.

Sapolsky, R.M.(1992). *Stress, the aging brain,and the mechanisms of neuron death*. Cambridge,MA:MIT Press. Robert Sapolsky is one of the leading researchers and theorists interested in the role of hormones and brain function. This very readable text not only introduces the reader to the basic facts but also provides a provocative broth of ideas.

Squire,L.(1987). *Memory and brain*. New York: Oxford University Press.Larry Squire is perhaps the most visible cognitive neuroscientist studying brain mechanisms underlying memory. This monograph is the best single volume describing what is known about the organization of the brain and memory.