2 The Hippocampus in Learning and Memory

2.1 INTRODUCTION

The human hippocampus is a small structure, about the size and shape of a crooked pinkie finger and lying under the cerebral cortex (figure 2.1). There is one hippocampus on each side of the brain, and the two hippocampi come near to joining at the back. The word *hippocampus* is Latin for "seahorse," and

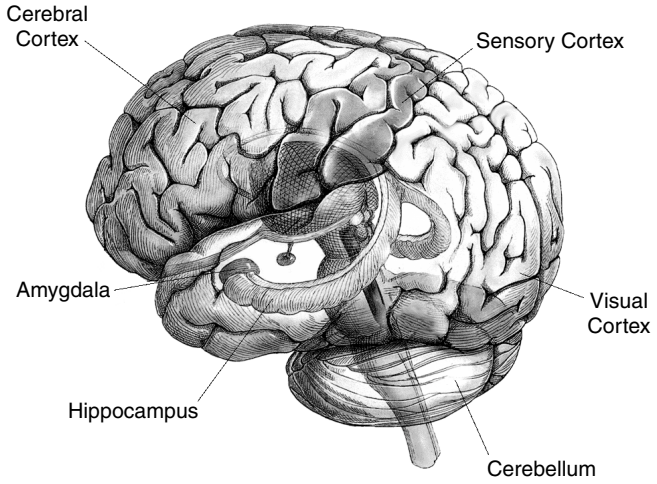

Figure 2.1 The human brain. The cerebral cortex is the wrinkled gray sheet (actually a thin layer of neurons) that covers most of the brain's surface; different areas within the cortex process and store different kinds of information. For example, sensory cortex is specialized to process tactile information, while visual cortex is a primary area for processing visual information. Near the base of the brain is the cerebellum, which is involved in coordination and fine control of movement. Buried under the temporal (or side) lobe of the cortex are the hippocampus and the amygdala, two structures that are involved in the acquisition of new memories. Whereas the amygdala seems critical for the emotional content of memories, the hippocampus may function as a memory gateway, determining which particular episodes and facts enter into long-term storage in cortex. (Adapted from Bloom, Lazerson, & Hofstadter, 1985, Figure 7.5, p. 185.)

the earliest known written description of the structure notes the similarity in appearance: "In its length [the structure] extends toward the anterior parts and the front of the brain and is provided with a flexuous figure of varying thickness. This recalls the image of a Hippocampus, that is, of a little seahorse."[1] Indeed, the human hippocampus does look like a seahorse, as shown in figure 2.2.

The hippocampi lie on the inner side of the temporal lobes—just below the temples along the sides of the head—in an area called the **medial temporal lobes** (figure 2.3A,B). In cross-section (figure 2.3C), the hippocampus appears as a pair of interlocking C-shaped structures (figure 2.3D). Some early neuroanatomists noted that this shape bore a resemblance to the horns of a ram. In fact, another name for the hippocampus is *cornu ammonis,* or "Ammon's horn," after the Egyptian god Amon, who was often represented with a ram's head. This nomenclature survives in the current names for the subfields of the hippocampus, which are known as fields CA (*cornu ammonis*) 1 through 4. The close-up in figure 2.3D also illustrates important nearby structures, including the **dentate gyrus, subiculum, entorhinal cortex, perirhinal cortex, parahippocampal cortex,** and **amygdala.**

Primates have medial temporal lobes roughly similar to humans', while other mammalian species have analogous structures that are laid out somewhat differently. For example, rats and rabbits, whose cerebral cortex is proportionally much smaller than humans', have a hippocampus that begins near the top of the brain and curves around toward the base (almost like a large-scale version of the ram's horn analogy). Thus, the medial temporal

Figure 2.2 A seahorse.

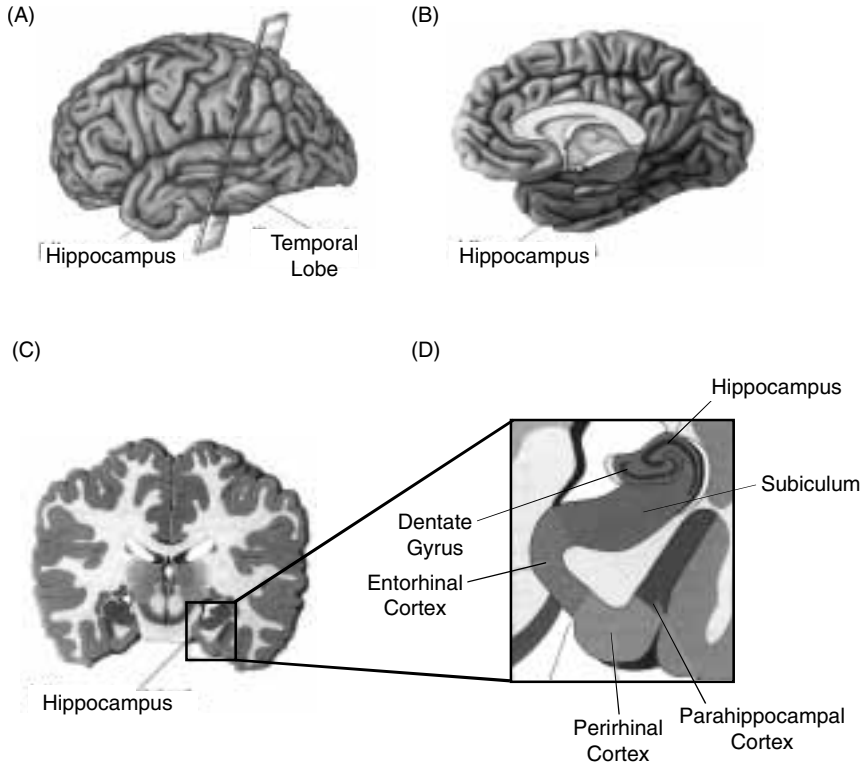

Figure 2.3 Structures in the medial temporal lobe. (A) A lateral (side) view of the intact human brain, showing one temporal lobe. The hippocampus is located on the inner (or medial) side of the temporal lobe. (B) A medial view, showing what the brain would look like if it were sliced down the middle and split into two halves. (C) If the brain were sliced as shown by the plane in (A), the hippocampus would be cross-sectioned, revealing (D) a series of interlocking C-shaped structures. The outer "C" is the hippocampus; the inner "C" is the dentate gyrus. Beyond the hippocampus lie the subiculum, entorhinal cortex, and other associated cortical areas. (Adapted from Bear, Connors, & Paradiso, 1996, Figure 19.7, p. 531.)

concept doesn't apply so well to these animals. In this book, *we use the term* ***hippocampal region*** *to refer to a subset of medial temporal structures: hippocampus, dentate gyrus, subiculum, and entorhinal cortex.* The **fimbria/fornix,** a fiber pathway connecting the hippocampus to subcortical structures, is often included as part of the hippocampal region as well. This definition of the hippocampal region applies equally well to any mammal, regardless of the specific anatomical layout of the individual structures. However, the exact functions of the hippocampal region remain a subject of contentious debate. Most

neuroscientists now agree that the hippocampus has something to do with learning and memory, but there is little consensus about what exactly the hippocampus is doing when we learn and store new memories.

In this chapter, we review current knowledge about hippocampal-region function. We start with a brief description of the memory impairments in humans with damage to the hippocampal region and then describe some classic behavioral impairments in animals with analogous brain damage. Some commonalities emerge to unify human and animal studies, but there are as many open questions as apparent answers.

It is important to note at this point that what follows is *not* a comprehensive review of the empirical literature on the hippocampal region. Rather, it is a selective review of those aspects of this literature that are most relevant to the subsequent discussion of computational models of the hippocampus and learning.

2.2 HUMAN MEMORY AND THE MEDIAL TEMPORAL LOBES

Much of our understanding of the hippocampal region's role in learning and memory comes from individuals who have suffered damage to the medial temporal lobes. In some rare cases, this damage is so circumscribed that it is almost possible to consider these individuals as having localized damage to the hippocampal region. More often, the damage is diffuse and involves other nearby structures, clouding the picture. By looking at a variety of individuals with a variety of patterns of damage, scientists are trying to build up a picture of what specific impairments follow hippocampal-region damage.

Medial Temporal Lobe Damage and Memory Loss

One of the most famous individuals with hippocampal-region damage was a young man who, to protect his privacy, is publicly known only by his initials, HM.[2] HM suffered from severe epilepsy, which was not ameliorated by drugs. The seizures were so frequent as to be incapacitating and life-threatening. In 1953, when HM was 27 years old, his doctors decided to try an experimental procedure: Since HM's seizures originated in his hippocampi, there was a possibility that surgical removal of the hippocampi would stop seizures from occurring. Doctors removed an 8-centimeter segment from each of HM's temporal lobes, including two-thirds of each hippocampus, as shown in figure 2.4. HM's seizures were indeed alleviated by the surgery, but it soon became apparent that there was a terrible cost: HM's ability to acquire new information had been devastated.

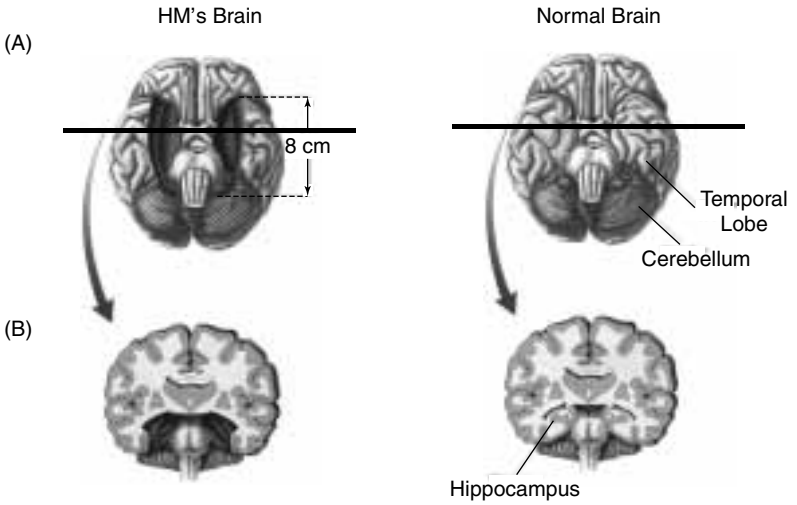

Figure 2.4 (A) A view of the brain from below, showing HM's lesion (left) and a normal brain (right). HM's lesion, involved removal of the medial temporal lobe from both sides of the brain. (B) A cross-section through the brain, with the cut at the position indicated in (A), shows HM's lesion (left) and a normal brain (right). (Adapted from Bear, Connors, & Paradiso, 1996, Figure 19.6, p. 529.)

Although HM's intelligence, language skills, and personality are largely as they were before the surgery, he has essentially no memories for any events from the last five decades. HM does have a reasonably normal memory for events that occurred at least two years before his surgery, but he does not remember subsequent events, such as the Vietnam War or the death of his father in 1967. Although he can participate in a conversation, a few minutes later he will have lost all memory of it. He cannot learn the names or faces of people who visit him regularly. Even the doctors and psychologists who have worked with him for over 45 years must reintroduce themselves to HM each time they meet. Since HM himself has aged since his surgery, he does not even recognize his own face when he is shown a current picture of himself. HM is painfully aware of his own problems and has described his life as constantly waking from a dream he can't remember: "Every day is alone in itself, whatever joy I've had and whatever sorrow I've had."[3]

HM's condition is known as **anterograde amnesia,** the inability to form new memories. In the years since HM was first tested, it has also become clear that some kinds of learning have survived, particularly his ability to learn new skills. We now know that although HM's damage included much of the temporal lobes, it is the damage to his hippocampus and the surrounding brain regions that is responsible for his anterograde amnesia.

The effects of HM's surgery were so debilitating that bilateral temporal lobe removal is now no longer used as a treatment for epilepsy. Unilateral removal, which removes the hippocampus and other parts of the medial temporal lobe from only *one* side of the brain, may still be done in cases of severe epilepsy; this usually results in a much milder memory impairment than seen in HM.

There are, however, other syndromes (also called **etiologies**) that can cause bilateral damage to the hippocampal region. For example, another famous patient, known by his initials RB, became amnesic following a loss of oxygen to his brain during heart bypass surgery. He showed the same general pattern of memory impairments as HM, although RB's amnesia was much less severe.[4] RB died a few years later, and he donated his brain to research so that scientists could better understand the cause of his amnesia. RB's hippocampus did indeed show extensive cell death, but this was limited to the CA1 subregion of the hippocampus (figure 2.5). The case of RB suggested that damage limited to the hippocampus was sufficient to disrupt

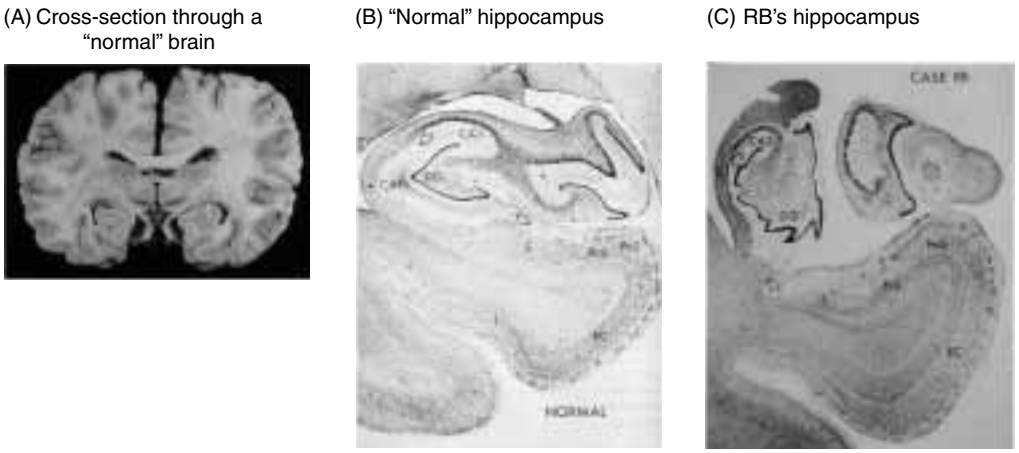

Figure 2.5 RB's lesion was limited to subfield CA1 of hippocampus. (A) A cross-section through the normal brain. (B) A close-up of a cross-section of the hippocampus in a normal brain. Information-processing cells, called neurons, are visible as dark areas. Cells in the dentate gyrus (DG) form one interlocking "C"; the hippocampus (including CA1 and CA3) forms another. CA1 neurons are in the area between the two arrowheads. (C) In RB's hippocampus, CA1 neurons have degenerated, visible as a lack of dark areas between the two arrowheads. The dentate gyrus, hippocampal field CA3, and the nearby subiculum (S) are largely intact, though warped slightly out of position. (Reprinted from Gazzaniga, Ivry, & Mangun, 1998, Figure 7.15.)

memory. Larger lesions do generally cause larger disruptions, accounting for the relatively worse amnesia in HM, who had a much larger lesion than did RB.

Transient loss or reduction of oxygen (called **anoxia** or **hypoxia**) is a frequent cause of amnesia, because hippocampal cells seem particularly sensitive to oxygen deprivation. This can occur during stroke and cardiac arrest, as well as near-drowning, near-strangulation, and carbon monoxide poisoning. Another etiology that can result in amnesia is **herpes encephalitis,** which occurs when the common herpes virus enters the brain and attacks nerve cells there; again, the hippocampal region appears especially vulnerable. A small degree of hippocampal damage occurs in the course of normal aging, and this damage is accelerated and magnified in the early stages of Alzheimer's disease, leading to memory failures. Damage to other parts of the brain can also sometimes cause anterograde amnesia,[5] possibly because damage to these structures interferes with the normal working of the hippocampus; we will return to this issue in later chapters.

In all these cases, *damage to or disruption of the hippocampal region may cause anterograde amnesia: a devastating loss of new memory formation, with relative sparing of intelligence, personality, skill learning, and old memories.* This is why we and others have characterized the hippocampal region as functioning much like a gateway to memory.

Anterograde Versus Retrograde Amnesia

Even a person with normal memory does not remember everything that has ever happened to her. She may have excellent memory for everything that happened to her today and relatively complete memory for everything that happened this week. But ask her what she had for lunch last Thursday or where she was on the morning of May 29, 1986, and unless those events were somehow significant, chances are she will have forgotten. Figure 2.6A schematizes this pattern of normal memory and forgetting: near complete memory for recent events and a gradual decrease in memory of progressively older events. Most people have only a few memories from as far back as infancy.

Using this schematic, figure 2.6B shows one way to schematize pure anterograde amnesia: The individual has normal memory for events from birth through childhood up to the time of the trauma; no memories are formed after the time of the trauma. Note that this does not imply that a person with anterograde amnesia remembers 100% of his childhood—just that he remembers it fully as well as a person with no memory problems.

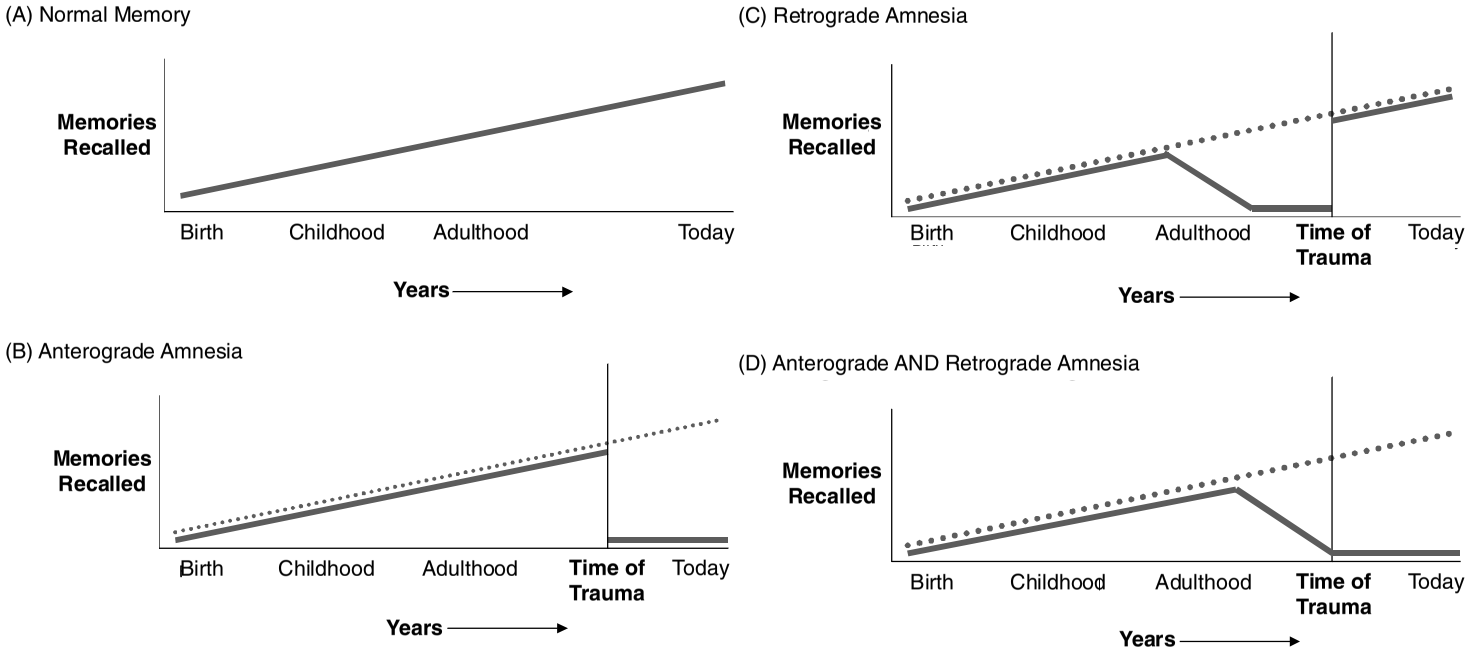

Figure 2.6 Schematic of memory and amnesic syndromes. (A) Normally, we have better and more complete memory for recent events than for events that happened in the distant past. We may remember every event that occurred today, most that occurred yesterday, and so on until we have very few memories of early childhood. (B) In pure anterograde amnesia, there is sparing of memories from events that occurred before the trauma but a near complete loss of the ability to remember events that have occurred since the trauma. For example, a person who suffers trauma in early adulthood would show normal memory for all events up until the time of the trauma but little or no memory for any events that occurred after the trauma. (C) In pure retrograde amnesia, there is loss of memory for events before the trauma. Events that occurred just before the trauma may be completely lost, and the loss becomes proportionally less for earlier events until at some point (possibly a year or two before the trauma), memory is as complete as normal (dotted line). Memories of events since the trauma are normal. (D) Most commonly, individuals with medial temporal lobe damage may show severe anterograde amnesia with some retrograde amnesia for events before the trauma. The exact extent and severity of retrograde and anterograde amnesia depend on the precise lesion and are different for every individual.

An alternative kind of memory impairment is **retrograde amnesia,** a loss of memory from before the trauma, with relative sparing of new memory formation. The slope in figure 2.6C illustrates the specific kind of forgetting in retrograde amnesia: There is little or no memory for events that happened immediately before the trauma, relative sparing of events from the distant past, and a smooth gradient in between.

It is important to note that retrograde amnesia is not the kind of memory loss that is often dramatized in movies, such as Alfred Hitchcock's *Marnie*, in which someone forgets not just events but her very identity. This kind of forgetting (sometimes called **fugue**) is extremely rare in real life. More commonly, memory loss may be restricted to a particular period of time, such as the duration of a violent crime; this is called event-specific amnesia. Both fugue and event-specific amnesia are examples of **psychogenic amnesia:** memory loss due to psychological, not physical, trauma, which often resolves in time, particularly with the help of therapy.[6] Some cases of pure retrograde amnesia resulting from physical brain injury have been reported,[7] but more often, some degree of retrograde amnesia co-occurs with anterograde amnesia, as schematized in figure 2.6D.

HM, for example, shows poor memory for events during the few years prior to his surgery as well as for all events afterward. Figure 2.7A shows the results of a study testing remote memory in several individuals who became amnesic following anoxia or a similar event between 1976 and 1986.[8] The study took place in 1986 and 1987, when the amnesic individuals were all about 50 years old. When the amnesic subjects were asked to recall details of news events that had occurred during the 1950s, the amnesics showed good recall of old information, remembering about as much information as same-age subjects with normal memory. Asked about the 1960s and 1970s, the amnesic subjects recalled progressively less information. Finally, asked about events from the 1980s, the amnesic subjects showed very poor memory; and, of course, they would remember little or nothing about more recent events that had occurred since the onset of amnesia. By contrast, the normal subjects tended to recall about 50% of the news events tested, and this performance was about the same for every decade. Figure 2.7B shows the same pattern of performance in normal and amnesic subjects who were asked to recognize faces of people who had become famous between 1940 and 1985.

The severe anterograde amnesia that follows hippocampal-region damage led to the hypothesis that the hippocampus was needed for the formation of new memories but not for the maintenance of older memories. The presence of retrograde amnesia in patients such as HM challenged this hypothesis;

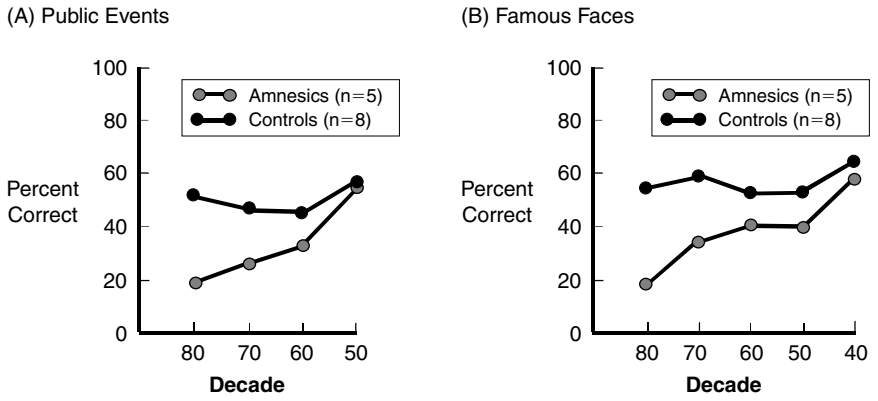

Figure 2.7 Individuals with anterograde amnesia also often show some degree of retrograde amnesia. (A) Five individuals with severe anterograde amnesia and eight control subjects with normal memory were tested for recall of public events during the years 1940–1985. All subjects were about 50 years old. Control subjects showed about 50% recall of the events from each decade. Amnesic subjects showed good recall for the earliest events (1950s) and progressively worse recall for later events. Events that occurred after the onset of amnesia (which varied between the years 1976 and 1986 for these five people) would show effectively no recall. (B) The same pattern of results is shown by these control and amnesic subjects when they were tested for recognition of faces of people who became famous during the various decades. (Adapted from Squire & Zola-Morgan, 1988, Figure 1.)

apparently, some older memories are indeed disrupted after hippocampal-region damage. However, this retrograde amnesia follows a reliable pattern: Memories formed just before the trauma are most likely to be disrupted; older memories are increasingly likely to survive. This suggests that while memories eventually become independent of the hippocampus, there is some **consolidation period** during which newly formed memories still depend on the hippocampus. Hippocampal-region damage during this time may devastate these newly acquired memories.

This idea of the consolidation period does not contradict the idea of the hippocampus as a gateway; it simply means that memories do not pass through the gateway instantaneously. There is some period of time during which recent memories still depend on the hippocampus; thus, destruction of the gate may impair recently acquired memories as well as preventing new learning. This pattern is common enough that, from now on, we will use the general terms **amnesia** and **amnesic** to refer to a syndrome involving severe anterograde amnesia with varying degrees of retrograde amnesia, usually produced by damage to the medial temporal lobes in humans, and corresponding to the effects of hippocampal region damage in animals.

Preserved Learning in Amnesia

There is yet another complication in the hypothesis that hippocampal-region damage disrupts new learning: Some kinds of memory can indeed survive hippocampal-region damage. For example, **short-term memory** is the kind of memory that lets us remember a seven-digit telephone number by constant rehearsal, although any interruption may result in loss of information from short-term memory. Short-term memory tends to be intact in HM and others with anterograde amnesia. This may be enough to allow HM to carry on an intelligent conversation with someone; but if the other person leaves the room and returns five minutes later, HM is likely to have no memory of the conversation.

Even within the domain of **long-term memory,** the kind of memory that lets us remember information over a period of weeks or years, individuals with anterograde amnesia do show some learning. For example, HM was trained on a new motor task, mirror drawing, in which he was asked to trace a figure like that shown in figure 2.8A while viewing the figure and his hand only through a mirror (figure 2.8B). This means that every time his hand moved left or right, it appeared in the mirror to go the opposite way.

Mirror drawing is quite difficult at first, although most people get progressively better with practice. HM became proficient at mirror drawing, and

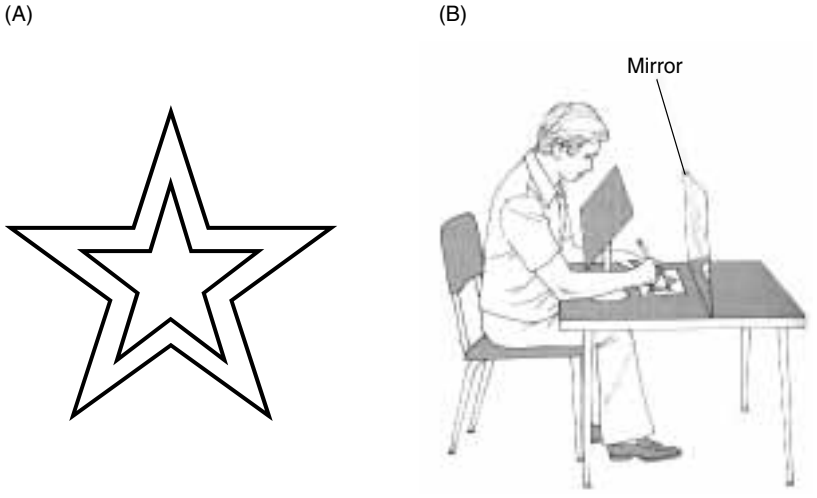

Figure 2.8 The mirror-drawing task. (A) Subjects are given this pattern and asked to trace it, keeping within the borders. (B) A screen is placed above the hand so that the subject can view progress only by watching a mirror, which reverses the apparent motion of the hand. (B is reprinted from Carlson, 1997, Figure 15.5, p. 457.)

his improvement was maintained over many days.[9] Despite this evidence of learning, HM had to have the task explained to him each time he started, because he would claim that he had never done such a thing before. While he remained unaware of his learning and of his past experiences with the task, HM's speed and accuracy in mirror drawing improved with each practice trial, much like those of a person with normal memory. Other individuals with anterograde amnesia show the same kind of improvement with practice,[10] suggesting that motor skill learning is generally spared after hippocampal-region damage.

Other kinds of skills can also be learned by individuals with amnesia. One example is the **figure completion task.** Subjects are shown a fragmented version of a line drawing and asked to name the object; if they fail, they are shown successively more complete versions of the figure until they can name it (figure 2.9). If subjects are retested an hour later, normal subjects will recognize the figure earlier—based on a more incomplete drawing—than they did previously. This effect holds even if there is an interval of many months between test sessions.

Figure 2.9 One test of perceptual learning (priming) involves picture fragments. Subjects are shown fragmented pictures (top) and asked to name the figure. If the subject cannot, progressively more complete versions are shown until the subject's guess is correct or the complete picture is shown (bottom). Later, the procedure is repeated; subjects tend to recognize the figure earlier (on the basis of a more fragmented picture) even if several months have passed since the original testing session. This implies some memory of the original figure, and this kind of learning is often preserved in amnesic subjects. (Reprinted from Gollin, 1960, Figure 1, p. 290.)

When HM was given this test and was then retested an hour later, he also showed considerable improvement from his first testing session, despite having no explicit recollection of having seen the figure before. Four months later, he still showed improvement over his initial performance. Although HM's testing performance at both intervals was worse than normal performance, it is clear that even in the absence of explicit recall of the experimental task HM showed unmistakable evidence of learning.

The figure completion task is a form of learning known as **priming,** which occurs when people find it easier to process a particular stimulus that they have seen before. Many different forms of priming have been shown to be intact in amnesic individuals, including priming for novel geometric patterns, faces, and the melodies and words of songs—all without a conscious memory of ever having seen or heard the stimuli before.[11]

All these kinds of learning that are spared in amnesia seem to have two features in common: First, they are incrementally acquired with practice. Second, they can be viewed as skills or habits that involve executing a procedure. This general class of learning is often called **procedural memory.** It includes everyday skills such as tying a shoelace that are well-learned and easy to perform but quite hard to describe verbally. Procedural memory is largely spared in anterograde amnesia.

By contrast, the kind of memory that is lost in HM and other amnesic individuals is called **declarative memory** because it is easily accessed by verbal recall. Declarative memory is often further subdivided into **episodic memory,** which is memory for specific (often autobiographical) events, and **semantic memory,** which is memory for facts such as vocabulary items or general knowledge about the world.

A simple heuristic is to define declarative memories as *knowing that* something happened, while procedural memories involve *knowing how* something is done. The cases of HM and others like him suggest that declarative memory depends critically on medial temporal lobe structures (such as the hippocampal region), while procedural memory may depend more on other brain structures. This distinction can be schematized as in figure 2.10, and it has been suggested that each kind of memory may depend primarily on a particular brain structure (or set of structures).*

*Recent studies have suggested that while episodic memory may depend primarily on the hippocampus, semantic memory may depend more on other, nearby structures such as the parahippocampal cortices (Funnel, 1995; Gaffan, 1997; Vargha-Khadem et al., 1997; Mishkin, Vargha-Khadem, & Gadian, 1998, cf. Squire & Zola, 1998).

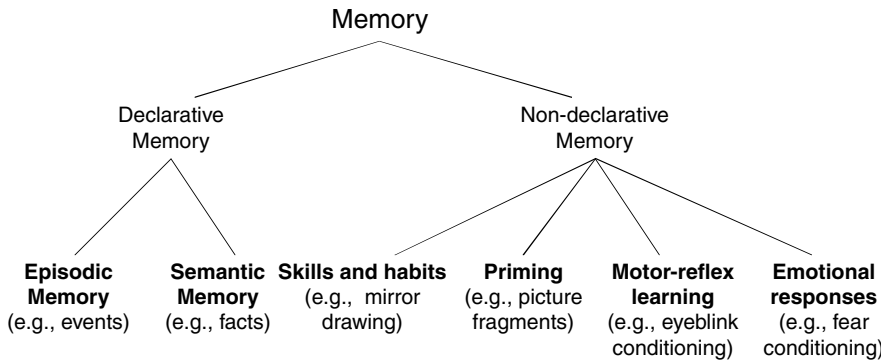

Figure 2.10 Taxonomy of memory proposed by Larry Squire and colleagues (after Squire & Zola-Morgan, 1988; Squire & Knowlton, 1995). Declarative memory consists of items that are easy to verbalize and generally accessible to conscious recall; this includes episodic memory of autobiographical events and semantic memory including vocabulary and general knowledge of the world. Nondeclarative memory is everything else, including skill and habit learning, priming, and conditioning—learning of reflexive or emotional responses to stimuli that habitually predict reward or punishment. Medial temporal lobe damage may devastate the acquisition of new declarative memory, while nondeclarative memory may be largely spared. This leads to the proposal that the medial temporal lobes are critical for forming new declarative memories, while nondeclarative memories may depend on other brain structures.

However, yet again, the picture is not quite as simple as it sounds. Increasingly, studies suggest that some kinds of procedural learning are indeed disrupted after hippocampal-region damage.

2.3 ANIMAL LEARNING STUDIES OF HIPPOCAMPAL FUNCTION

Neuropsychological studies of human memory impairments are based primarily on examinations of those rare individuals who have sustained brain damage to the medial temporal lobes. However, damage in these cases is seldom limited to just a single region of the brain. Although the hippocampal region is especially vulnerable to injury through stroke, anoxia, and encephalitis, these etiologies can cause diffuse damage. Thus, an individual may have memory impairments that reflect damage to regions beyond the medial temporal lobe. Further, even within the medial temporal lobe, damage is rarely complete. Some amnesic individuals have partial sparing of behaviors that do depend on the medial temporal lobes. Thus, no two amnesic individuals are exactly alike, either in their memory disorders or in the exact extent of their brain damage.

However, by also doing research on animals, scientists are able to create precise lesions and be certain to remove certain brain regions completely

while causing little or no damage to other brain regions. Thus, animal models of amnesia can avoid some of the problems inherent in human research.

It is important to note that most careful studies compare lesioned animals against specific **control** animals, not against normal animals. A control animal is one that has undergone the same surgical procedure as the lesioned animal—but without the actual lesion; the result is sometimes called a "sham lesion," and the animal is referred to as a **sham control.** For example, a brain lesion may be created by anesthetizing an animal, opening the skull, and removing small pieces of the brain by **ablation** (cutting out brain tissue) or **aspiration** (sucking out brain tissue). Since the hippocampus is buried under the cortex, this kind of procedure usually entails damage to some of the cortex that lies between the skull and the hippocampus. Thus, a control procedure for a hippocampal lesion might be to operate on a second animal in the same way but stop just short of damaging the hippocampus. Thus, any abnormal behavior in the lesioned animal would reflect hippocampal damage, not merely damage to overlying brain tissue, or else the control animals would show the same effect. A more modern lesion technique involves lowering a syringe into a precise brain location and injecting a **neurotoxin** that destroys neurons (brain cells) near the injection site. A sham control for this lesion would involve anesthetizing the animal, lowering a syringe, and injecting a comparable amount of harmless saline. Thus, the lesioned and sham control animal should be identical in every way except for the loss of neurons in the lesioned animal. In this case, any abnormal behavior in the lesioned animal can be safely attributed to the loss of neurons rather than to the general effects of anesthesia and surgery.

The use of proper controls is another advantage of animal research over human research. Humans generally experience hippocampal-region damage as a result of stroke, disease, anoxia, or other brain trauma. It is difficult to envision a proper control for such a subject, so researchers often make do by comparing amnesic subjects against individuals of the same sex and age who have never had any brain injury. But this leaves open the possibility that memory impairments in the amnesic subjects might be the result of damage outside the hippocampal region.

However, animal research presents its own problems. The most obvious deficit in human amnesia is a failure of declarative memory that is usually evaluated by asking subjects to recall or recognize information they have seen previously. It is not so easy to assess declarative memory in animals; obviously, a researcher cannot ask a rat whether it remembers what it did a few hours ago.

One approach to evaluating animal memory has been to test whether animals have something like an episodic memory for specific events. This has been a major focus of study in nonhuman primates and, more recently, in rats. Another approach has been to observe animals with hippocampal damage and assess what behaviors are most devastated; researchers then try to understand what these behaviors have in common with the amnesic syndrome in humans. A third approach is to consider simple learning behaviors that are common to humans and other mammals and attempt to understand the pattern of impairment after hippocampal-region damage across species. We give some examples of each kind of approach below.

Episodic Memory in Animals

Many studies of learning have been conducted using monkeys because they are more similar to humans than any other animal, in terms of both cognitive abilities and brain anatomy. Therefore, if any animal can be argued to have episodic or declarative memory, it should be monkeys.

One of the most commonly used tests of memory in the monkey is called **delayed nonmatch to sample (DNMS),** and it is illustrated in figure 2.11.[12] The monkey faces a table that has three small wells. First, the monkey sees a sample object, such as a red ball, covering the center well. Then a screen covers the wells for a short delay. When the screen is removed, there are two

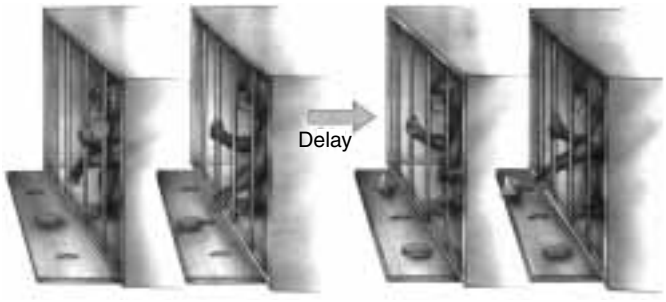

Figure 2.11 The delayed nonmatch to sample (DNMS) task. The monkey sees three wells; the center is covered with a small object (far left); the monkey displaces this object to get a food reward (center left). Next, there is a short delay, usually 5 to 60 seconds, during which the wells are hidden by a screen. When the screen is removed, the two outer wells are covered (center right). One well is covered with the previously seen (sample) object; the other is covered with a new object. The monkey is allowed to displace one object. If it displaces the new object, it obtains a small food reward. The nonmatch to sample task is performed well by monkeys with hippocampal-region lesions if the delay is short. With increasing delays, lesioned monkeys show impairments. (Reprinted from Bear, Connors, & Paradiso, 1996, Figure 19.9, p. 532.)

objects on the table, covering the left and right wells. One of the objects is the sample object that was previously seen, and one is new. There is a food reward under the new object. The monkey must learn to choose the new object to get this reward. In other words, the monkey learns to choose the object that does not match the sample object (hence the task's name).

With extensive training, normal monkeys can learn this task quite well, even when the task involves delays of up to ten minutes. Because the monkey's choice depends on a single event from several minutes before, this task appears to require episodic memory of the sample presentation. Thus, it seems to be a good example of the kind of task that might be disrupted by hippocampal-region damage, based on related deficits in amnesic humans with similar brain damage.

Indeed, DNMS is severely impaired in monkeys with lesions of the hippocampal region, including hippocampus, dentate gyrus, subiculum, and the adjacent entorhinal and parahippocampal cortices.[13] Interestingly, lesioned monkeys are impaired at the task only if there are delays longer than a few seconds. If there is no delay between sample and choice, the lesioned monkeys are practically normal. Thus, the lesioned monkeys, like human amnesics, appear to have intact short-term memories but an impaired ability to form new longer-term memories that span delays of many minutes. In fact, when the same DNMS task was applied to human amnesics, the same pattern of results appeared: The amnesic subjects performed as well as normal subjects when there was little or no delay, but performance grew much poorer at longer delays.[14]

Later, a variety of different monkey studies showed that the exact lesion extent was critical; in fact, lesion limited to the hippocampus alone produced little or no impairment on DNMS, except at the longest delays.[15] These findings highlighted the importance of knowing which structures were damaged and suggested that different structures within the hippocampal region might be performing subtly different functions. We will return to this topic in chapter 9.

Recently, several studies have attempted to demonstrate episodic learning in other species, including rats.[16] In a rodent version of DNMS, a rat is given sample exposure to an odor and later presented with a choice between the same odor and a novel odor; response to the novel odor is rewarded. Again, lesion of the hippocampus does not impair this task, although lesions of the surrounding cortices do lead to an impairment if there is a long delay between sample and choice.[17]

Together, these studies suggest that, in animals and humans, the hippocampus itself may not be strictly necessary for recognition, at least with short delays. It is possible, however, that other more complex forms of recognition memory do require the hippocampus.

Spatial Navigation and the Hippocampus

Given the difficulties in developing direct analogs of episodic memory tests for animals, an alternative approach is to determine which kinds of learning are most severely disrupted by hippocampal-region lesion in animals and then attempt to relate that back to human amnesia.

In rats, one of the most striking features of the hippocampus is the existence of **place cells,** neurons that exhibit electrical activity when the animal is in a particular region of space.[18] For example, suppose a rat is allowed to wander a small, square chamber while an experimenter records the activity of place cells in hippocampal subfield CA1. One cell may become strongly active when the rat is along one edge of the chamber (figure 2.12A), while another nearby cell might become strongly active when the rat is on the opposite side of the chamber (figure 2.12B). With enough place cells, the entire

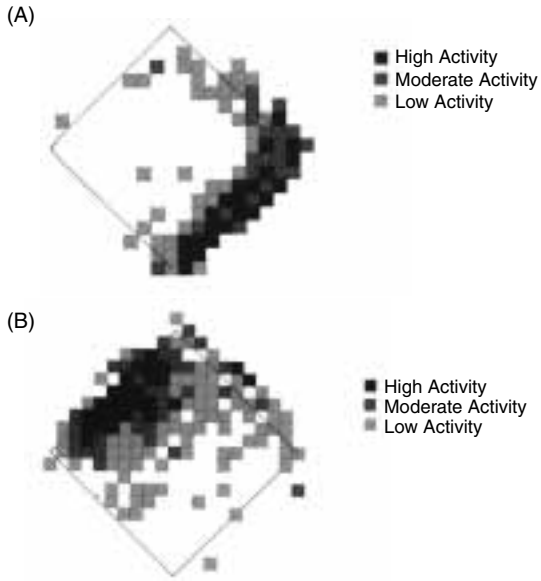

Figure 2.12 Place cell recordings: traces of activity of individual neurons in hippocampal subfield CA1. (A) A rat was allowed to wander freely through a square chamber, and at each point, the degree of activity was recorded from a single CA1 neuron. Dark spots show locations where the neuron was very active; white areas are locations where the neuron was essentially inactive. The neuron was most active when the rat was in a particular area (near the southeast wall) and nearly inactive when the rat was on the far side of the chamber from the preferred location. (B) Another nearby neuron responded most strongly when the rat was near the northwest wall. Given recordings from enough CA1 neurons, it would be possible to deduce the rat's position just on the basis of the pattern of activity. (Adapted from O'Keefe, 1983, Figures 2 and 3.)

chamber is covered, and it is possible to deduce where the animal is simply by monitoring the pattern of cell activity.[19] These and similar findings lead to the hypothesis that the hippocampus is involved in building a spatial map of the environment, which an animal can use to navigate through its surroundings.[20]

If this is so, then spatial learning should be severely disrupted by hippocampal-region damage. In fact, rat data show just this. One technique for studying spatial learning in rats, developed by Richard Morris, involves a **water maze**[21] in which a rat is placed in a circular pool filled with opaque liquid (often water with a little powdered milk). Hidden somewhere in the pool is a small platform, just under the surface of the water. As the rat swims, it will eventually stumble across the platform and escape from the water. On each trial, the experimenter puts the rat into the pool at a new starting position and records how long it takes the rat to locate the escape platform. Normal rats will quickly learn to take short, relatively direct paths to the hidden platform (figure 2.13A). Further studies showed that the normal rats were navigating on the basis of visual cues around the room; if the cues were removed or moved, the rats would not be able to locate the platform.

By contrast, rats with hippocampal lesions never seem to learn the location of the platform.[22] Instead, on every trial, they swim around randomly until they happen upon the platform (figure 2.13B). The lesioned rats can learn that there is an escape platform; if the platform is raised slightly so as to be visible above the water, the lesioned rats swim to it quickly.[23] What the

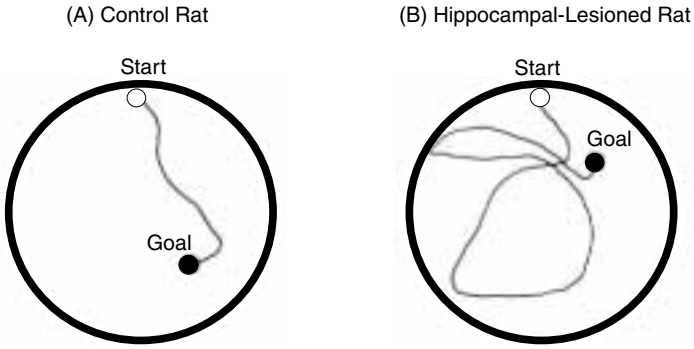

Figure 2.13 The water maze: Rats are placed in a pool at a start location (light circle) and swim to a hidden escape platform (dark circle). (A) After 28 trials, a normal rat swims to the hidden platform by a nearly direct route. (B) After 28 trials, the hippocampal-lesioned rat still swims randomly around the pool until it happens to find the platform. Apparently, the lesioned rat is unable to use visual cues around the room to navigate to the location of the hidden platform. (Adapted from Morris, 1983, Figure 4.)

lesioned rats seem unable to do is to integrate visual information to figure out where they are relative to the hidden platform and how to navigate from one point to the other.

These results and results from other spatial tasks, such as maze learning, show that spatial learning is devastated in rats with hippocampal-region damage. How does one reconcile this result with human data? What do spatial learning in rats and declarative memory in humans have to do with each other? One answer is that each is a task of paramount importance to the species. Rats are, by nature, foraging animals. The ability to navigate to a food source and return home afterward is critical to the rat's survival. By contrast, the ability to form declarative memories of autobiographical events seems to be at the very core of human existence, which focuses on our experiences and the ability to communicate these experiences to others.

But there is another way of looking at things, and that is to question the very nature of spatial learning. What is a place? One definition is that a place is a collection (or configuration) of views. When we stand in one spot and look north and stand in the same spot and look south, those two views should be integrated into a unified percept of the current location so that the next time we approach that spot (from any angle), we recognize where we are. In addition to visual cues, there may be auditory, olfactory and tactile cues, as well as memory of the route by which we reached the spot and what happened when we got there. All this information should be combined into the memory of a "place." Thus, spatial learning may be a special case of configural learning: the ability to bind elements together into a single complex memory.

Viewed in this way, there is a certain parallel with declarative memory. A declarative memory also consists of many separate components that are unified into a single complex memory. For example, the memory of a party might include representations of the locale, the food served, the attendees, some interesting conversations, and so on. These components are collected (configured) into the declarative memory of the event. Thus, declarative memory and spatial memory may share some important features, such as the need to configure information into complex memories and to retrieve them later on the basis of just a subset of the original information (such as a fragment of an autobiographical memory or a view from only one starting point in the pool). Several prominent theories of hippocampal-region function have focused on this idea, and we will review some of these in the context of hippocampal models in chapter 6.

For now, it is important to note that the same neurons that show spatial responses during a spatial task (e.g., figure 2.12) will also respond during a

nonspatial task, such as learning to respond to one odor but not another.[24] Thus, it seems that hippocampal neurons encode whatever information is important to the current task, be it spatial or otherwise. Some kinds of task, such as spatial learning and declarative learning, depend critically on this information encoded in the hippocampus; thus, they appear to show the largest deficit following hippocampal lesion. Therefore, even if the hippocampus is not a spatial processor *per se*, spatial learning remains an important domain for studying dysfunction after hippocampal-region damage.

Importance of Well-Characterized Learning Behaviors

Studies of delayed nonmatch to sample in primates and spatial navigation in rodents have yielded a tremendous data bank of information on the role of the hippocampus in memory. But to fully understand the role of the hippocampus in a specific memory task, we need to begin with a clear understanding of how an animal solves the task normally; only then can we characterize and measure what has changed once the hippocampus is damaged.

Unfortunately, in such complex tasks as episodic memory, DNMS, and spatial navigation, neither the behavioral nor the neurobiological mechanism is well understood. While these types of memories are among the most clearly devastated following hippocampal-region damage, the problem for modeling is that psychological studies of these behaviors have not yet led to detailed mechanistic theories or models. That is, psychologists don't really understand how declarative or spatial memories are stored and recalled. Without a good theory of these behaviors to begin with, it is difficult to imagine how they could be mapped onto brain circuits. For this reason, many researchers have argued that it is advantageous to study the hippocampus through simpler forms of learning in which we *do* have a clearer and deeper understanding of both the behavioral strategies used by animals and the essential brain structures involved. The next section discusses one example: classical conditioning.

2.4 CLASSICAL CONDITIONING AND THE HIPPOCAMPUS

One of the most basic forms of memory is **associative learning:** learning relationships between stimuli such as which stimulus predicts another or which pairs of stimuli tend to co-occur. One kind of associative learning is **classical conditioning,** often called **Pavlovian conditioning** after Ivan

Pavlov, the Russian scientist who first described it. Pavlov was a physician who was using dogs to study digestion. Each day, before feeding the dogs, Pavlov rang a bell. Soon, Pavlov noticed that the dogs would begin to salivate as soon as they heard the bell, even if no meat was given. Pavlov reasoned that the bell was a stimulus sufficient to produce salivation in anticipation of feeding—simply because the dogs had learned to associate the bell with the expectation of food. Since Pavlov's time, classical conditioning has received extensive study in normal animals and humans, as well as in animals and humans with various kinds of brain damage. The neural mechanisms for this kind of learning are relatively well understood, which means that it is possible to build precise theories of how memories are created and stored.

Classical conditioning can be obtained with a wide range of stimuli. All that is required is that there is a biologically significant stimulus, such as food or an electric shock (called the **unconditioned stimulus,** or **US**), that elicits an automatic, reflexive response (called the **unconditioned response,** or **UR**). A previously neutral stimulus, such as a tone or a light (called the **conditioned stimulus,** or **CS**), is repeatedly presented just before the US, until the CS alone can elicit a preparatory response (called the **conditioned response,** or **CR**). Figure 2.14 shows this concept schematically.

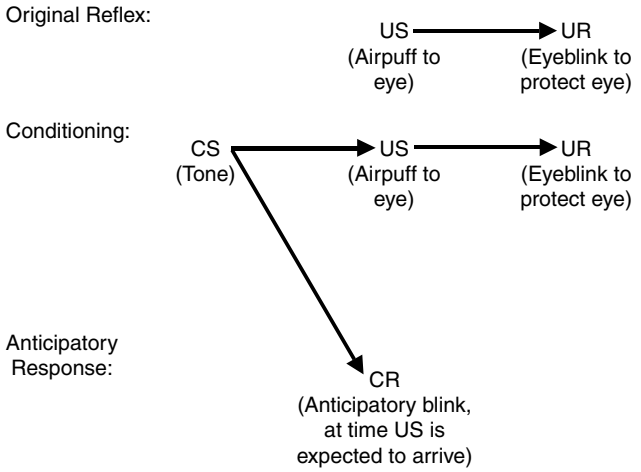

Figure 2.14 Schematic of classical conditioning. An unconditioned stimulus (US), such as an airpuff to the eye, elicits a reflexive, protective response, such as eyelid closure. This is the unconditioned response (UR). If the US is repeatedly preceded by a neutral stimulus, such as a tone or light (the conditioned stimulus, or CS), an association forms in which the CS predicts the US, and there is a conditioned response (CR) to the CS, such as an anticipatory eyeblink, timed so that the eye is fully closed at the expected time of US arrival.

All animals, including humans, exhibit classical conditioning, and the properties of this behavior are similar across all species. One popular form of classical conditioning is the rabbit eyeblink preparation.[25] The experimental apparatus is shown in figure 2.15A. The rabbit is given a mild airpuff or shock to the eye (the US), which elicits a reflexive, protective eyeblink (the UR). This US is repeatedly preceded by a neutral stimulus, such as a tone or a light (the CS). With enough CS-US pairings, the CS itself comes to elicit an anticipatory protective blink (the CR). Over time, the eyeblink CR will be timed so that the eyelid is maximally closed at the exact time of anticipated US arrival, as seen in figure 2.15B.

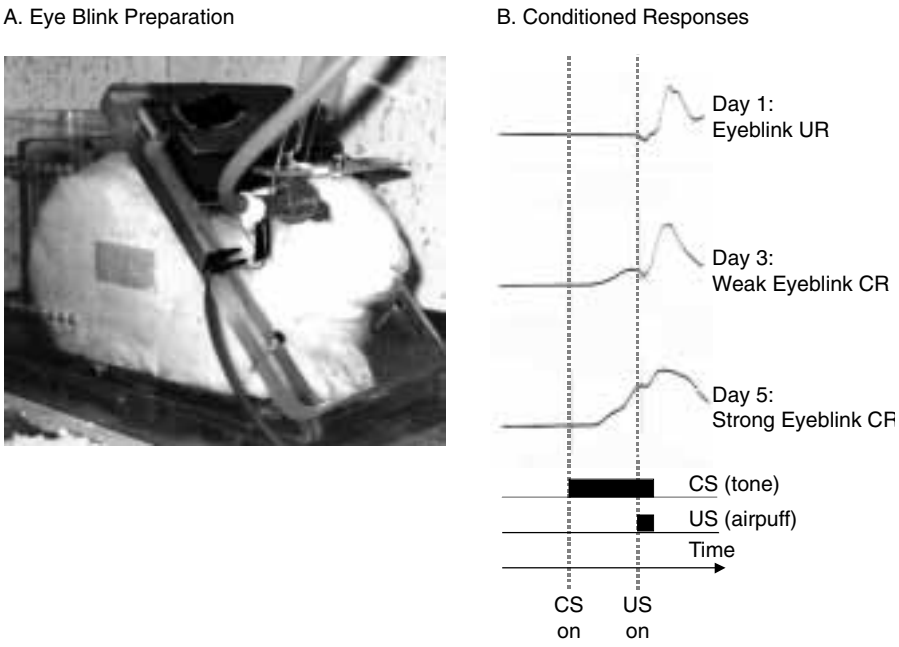

Figure 2.15 Rabbit eyeblink conditioning. (A) The rabbit is placed in a restraining box. A rubber hose delivers precisely timed puffs of oxygen to the right eye (US); these elicit protective eyeblinks (UR). If a previously neutral tone or light CS reliably precedes the US by a few hundred milliseconds, the rabbit develops an anticipatory eyeblink CR to the CS, so that the eye is closed at the time of expected US arrival. An infrared device measures reflectance off the eye, giving an index of eye closure. (B) On the first day of CS-US training, presentation of the CS evokes no eyeblink, but there is a strong blink UR in response to the airpuff US. By the third day of training, there is a small eyeblink CR in response to the tone, which partially closes the eye just before expected US arrival. By the fifth day of training, there is a strong CR, protecting the eye at the time of US arrival. (B is adapted from CR traces shown in Zigmond et al., 1999, Figure 55.13, p. 1430.)

Rabbits are often used for eyeblink conditioning experiments because they are content to sit quietly in a small restraining chamber for long periods of time during the procedure. In contrast, rats are more active animals and do not take well to such restraint. Lately, new procedures have been developed for rats in which the animal is allowed to move freely around a cage during conditioning.[26] Humans are also good subjects for eyeblink conditioning, since a human can be asked to sit still and is often given a movie to watch as entertainment during the experiment.[27] The procedure has even been adapted for monkeys.[28] In all cases, conditioning appears very similar across species, and so results found in one species can reasonably be expected to apply to others.

An obvious next question is whether conditioning survives hippocampal-region damage in animals and humans. On the surface, classical conditioning seems to be nondeclarative: It can be acquired over many iterative trials without any conscious memorization of the rules. In fact, all species tested so far, including invertebrates such as the octopus and the sea snail that do not even have a hippocampus, can display classical conditioning.[29] Therefore, it seems reasonable to expect that hippocampal-region damage should not eliminate classical conditioning. To a first approximation, this is indeed the case; however, it appears that the hippocampus, when present, does play an important but subtle role.

Hippocampal Lesions and Simple Conditioning

Early studies of the hippocampus and conditioning yielded puzzling, seemingly contradictory results. In rabbits, bilateral hippocampal lesions did not retard the rate at which the animal learns to give an eyeblink response to a single CS (figure 2.16).[30] In fact, in one study, the lesioned rabbits actually learned faster than normal rabbits![31] Nor did hippocampal lesions slow acquisition of an eyeblink CR in humans with hippocampal-region damage.[32] These results argued that the hippocampus is not necessary for eyeblink conditioning.

While behavioral studies were suggesting that the hippocampus did not mediate eyeblink conditioning, neurophysiological recordings were suggesting just the opposite. When the activity of single neurons in the hippocampus was recorded during conditioning, the neurons' activity became stronger as the CR was being learned (figure 2.17).[33] Not only did this hippocampal activity mimic the CR, but it also preceded the CR by about 40 milliseconds, suggesting that the hippocampus might be responsible for generating the signal that caused the eyelid to close in anticipation of the airpuff

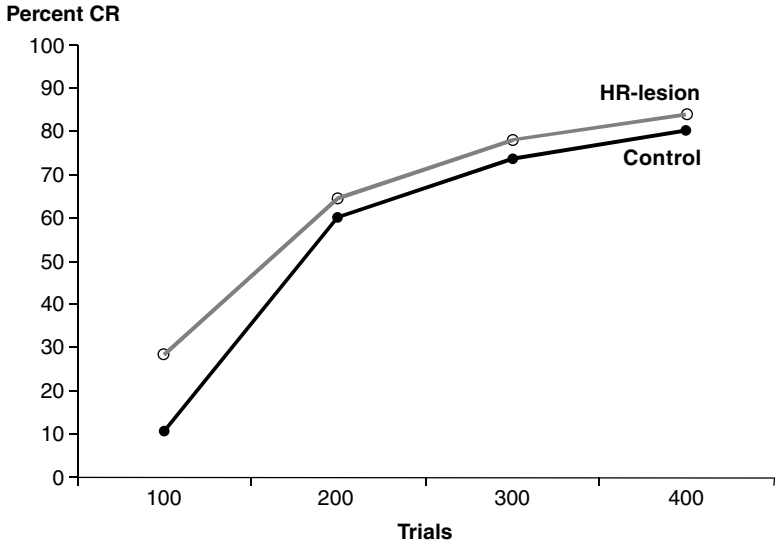

Figure 2.16 Eyeblink conditioning in rabbits is not slowed by hippocampal-region (HR) lesion. (Drawn from data presented in Allen, Chelius, & Gluck, 1998.)

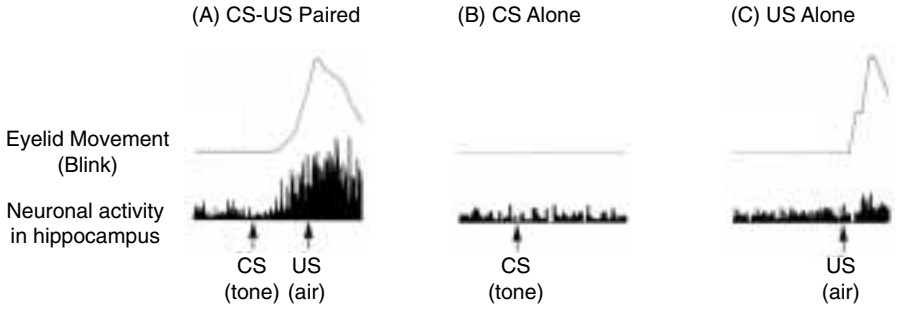

Figure 2.17 Pattern of activity of single neurons in the rabbit hippocampus during eyeblink conditioning. (A) After repeated pairing of a CS and US, the rabbit gives a blink (CR) to the CS, which precedes onset of the US and continues into the US period. Hippocampal neurons show increased activity during this CR and sustain that activity during the blink response. (B) By contrast, in an untrained rabbit, the CS evokes no blink response and no hippocampal activity. (C) If the US is presented alone, there is a reflexive eyeblink (UR) but no change in hippocampal activity. Thus, the hippocampal neuronal activity seems specifically to code for a CR: reflecting the CS prediction of US arrival. (Adapted from Berger, T. W., Rinaldi, P. C., Weisz, D. J., and Thompson, R. F. *Journal of Neurophysiology,* 1983, *50,* 1197–1219, as reprinted in Carlson, 1986, Figure 14.39, p. 586.)

US. Yet the hippocampus could be completely removed without impairing conditioning, as the behavioral studies had shown. So what was the purpose of this hippocampal activity?

One interpretation is that there is a subtle difference between whether a brain structure normally contributes to a particular behavior and whether it is actually necessary for that behavior. On the one hand, the ability of hippocampal-lesioned animals to acquire a CR indicates that the hippocampus is not *necessary* for eyeblink conditioning. On the other hand, the neurophysiological data show that, in the normal brain, the hippocampus is indeed *involved* in eyeblink conditioning.

This difference—between whether the hippocampus is actively involved and whether it is strictly necessary—turns out to be critical in understanding a great deal of data. It also emphasizes one of the dangers of basing too much theory on lesion data: Just because a behavior (such as eyeblink conditioning) *survives* lesion of a brain structure does not mean that that brain structure ordinarily plays no role. As a simple example, when walking, we normally integrate both visual cues and vestibular cues (our sense of balance) to keep upright. When we shut our eyes, we can still stand upright. Vision is not *necessary* for this behavior, but it normally contributes. The same seems to be true of the hippocampus: *The hippocampus may normally contribute to all learning, even those kinds of learning (such as simple classical conditioning) for which its help is not strictly needed.*

The Hippocampus and Complex Conditioning

What is the hippocampus doing during classical conditioning if its contributions appear to be irrelevant to learning a simple tone-airpuff relationship? Later studies showed that although the hippocampus was not needed for simple conditioning—learning that one CS predicted one US—it was indeed needed if the experimental procedure grew a little more complex. In the sections to follow, we describe two variations on the basic CS-US learning described above: trace and long-delay conditioning and sensory preconditioning. In each case, there is evidence that the hippocampal region plays an important role during Pavlovian conditioning.

Trace and Long-Delay Conditioning. One example of hippocampal-dependent conditioning is the trace conditioning procedure. In ordinary conditioning (often called **delay conditioning**), the CS lasts for a short period of time, usually about 300 milliseconds. At the end of that period, the US occurs, and the CS and US coterminate (figure 2.18A). In **trace conditioning,**

the CS does not last throughout the whole period until US arrival (figure 2.18B). Instead, there is a short interval between CS offset and US onset. To time the CR to coincide with US arrival, the subject must maintain a memory, or *trace*, of the CS during this interval. Trace conditioning generally takes an animal longer to learn than delay conditioning, but normal animals eventually master it.[34]

However, hippocampal lesion greatly impairs the ability to learn trace conditioning. If the trace interval is short (e.g., 300 milliseconds), lesioned animals can learn an eyeblink CR at the same speed as normal animals.[35] However, if the trace interval is increased to 500 milliseconds, the lesioned animals are strongly impaired (figure 2.18C).[36]

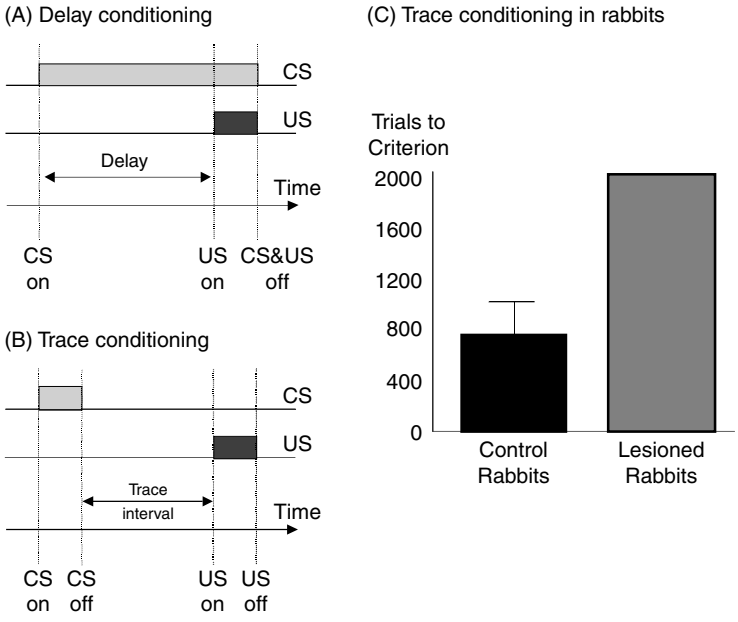

Figure 2.18 (A) In delay conditioning, the CS comes on some time before the US (e.g., 300 milliseconds) and remains on during the delay until US arrival. The CS and US coterminate. (B) In trace conditioning, CS offset occurs some time before US arrival. Some memory, or trace, of the CS must be maintained during the interval to allow generation of the CR at the time of expected US arrival. (C) With a long trace interval (500 milliseconds), control rabbits can reach criterion performance, responding to the CS on over 80% of trials, after about 800 CS-US training trials. By contrast, hippocampal-lesioned rabbits never reach this performance criterion, responding on only about 22% of trials, even after some 2000 training trials. (C is adapted from Figure 5 of Moyer, Deyo, & Disterhoft, 1990.)

Thus, the hippocampus appears to be involved in learning temporal relationships between CS and US, and this may be especially critical in trace conditioning, in which there is a gap between CS and US. This bears a resemblance to the finding in monkey DNMS studies that hippocampal lesions lead to impairments with long delays but not with short ones. Although DNMS and eyeblink conditioning seem superficially very different, the pattern of hippocampal-lesion impairments in each may reflect similar underlying mechanisms and a reliance on hippocampal-mediated temporal processing.

Sensory Preconditioning. **Sensory preconditioning** is another conditioning procedure that is disrupted by hippocampal lesion. This procedure involves three phases, as summarized in table 2.1. Animals in the Compound Exposure group are first given exposure to a compound of two stimuli, such as a tone and a light, presented together. Next, the animals are trained that one of the stimuli (say, the light) predicts a US (such as a blink-evoking airpuff); eventually, the animals give a blink CR to the light CS. Finally, in phase 3, the animals are tested with the tone. Normal animals will give a modest but detectable response to the tone in phase 3 (figure 2.19). This transfer depends critically on the exposure to the tone and light compound in phase 1; animals that are given separate (unpaired) exposure to the tone and light in phase 1 show little or no transfer and virtually no responding in phase 3.[37] Apparently, the compound exposure in phase 1 allows the animals to make a link between tone and light, so that the learning about the light transfers to the tone in phase 2.

The story is different for animals with hippocampal damage. Rabbits with hippocampal disruption (specifically, lesion of the fimbria/fornix) show no sensory preconditioning (figure 2.19).[38] Animals that are exposed to the compound show no more transfer in phase 3 than animals that are given exposure to the tone and light separately. It seems that the hippocampus is needed for learning the association between tone and light in phase 1.

Table 2.1 Sensory Preconditioning

Group	Phase 1	Phase 2	Phase 3: Test
Compound Exposure	Tone and light (together)	Light → airpuff ⇒ blink!	Tone ⇒ blink!
Separate Exposure (control group)	Tone, light (separately)	Light → airpuff ⇒ blink!	Tone ⇒ no blink

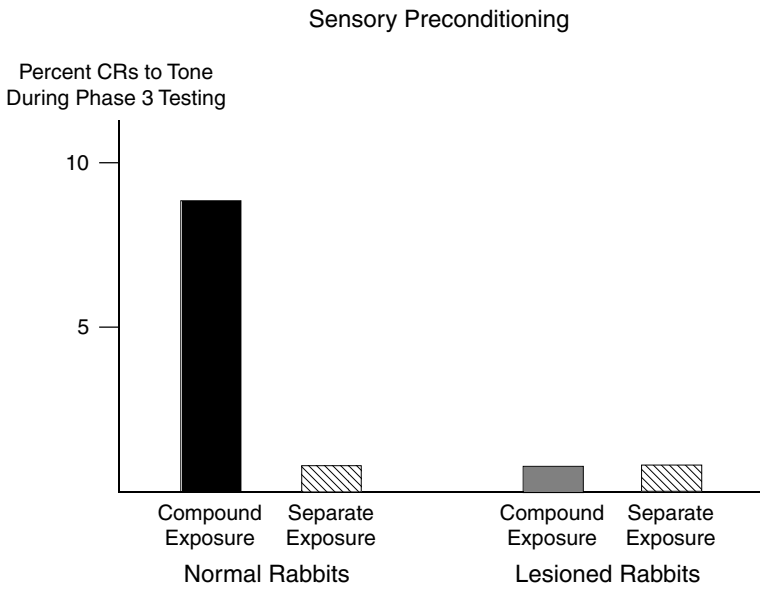

Figure 2.19 In sensory preconditioning, animals are given phase 1 exposure to a compound stimulus consisting of tone and light, presented together. In phase 2, animals are trained to respond to the light. In phase 3, animals are tested for their response to the untrained tone stimulus. Normal rabbits that are given compound exposure in phase 1 show some responding to the tone in phase 3. By contrast, normal rabbits that are given separate exposure to tone and light in phase 1 show little or no responding to the tone in phase 3. Rabbits with hippocampal-region damage (specifically, lesion of the fimbria/fornix) do not show sensory preconditioning; rabbits there are given compound exposure to tone and light in phase 1 show no more transfer than rabbits given separate exposure. (Drawn from data presented in Port & Patterson, 1984.)

Studies of sensory preconditioning and related phenomena suggest that the hippocampus is especially critical for learning that takes place in the absence of reinforcement (e.g., a US), even within a domain such as classical conditioning. Other conditioning studies have suggested that the hippocampus is critical for learning about *context* and about *configurations of stimuli. What all these tasks have in common is the need to represent relationships between stimuli that are independent of the associations between stimuli and reinforcement.* This idea has formed the basis for many influential theories of hippocampal-region function.[39] We will discuss these theories more fully in chapter 6.

2.5 IS A UNIFIED THEORY OF HIPPOCAMPAL FUNCTION IN LEARNING POSSIBLE?

The wide range of impairments following hippocampal-region damage—declarative memory in humans, spatial learning in rats, stimulus-stimulus learning in classical conditioning—has created a major puzzle for neuroscientists who are interested in specifying a precise function for the hippocampal region. This confusing state of affairs has led to many different theories or descriptions of hippocampal function. Unfortunately, many of these "theories" amount to little more than a description of some or all of the behaviors that are impaired by hippocampal-region damage. They tend to focus on one kind of behavior at the expense of explaining others. Claiming that the hippocampal region is involved in only declarative memory doesn't account for hippocampal-lesion impairments in sensory preconditioning, a behavior that clearly falls within the definition of nondeclarative motor learning. Claiming that the hippocampal region is a spatial processor doesn't account for the monkey data showing impairments in DNMS at long intervals—a task with no particular spatial component.

Attempts to relate lesion studies to particular behavioral functions have, in the past, been fraught with frustration. One prominent memory researcher, Richard Thompson, voiced this frustration when he and his colleagues wrote:

> In our view, this question [What is the function of the hippocampus?], as it is phrased, is not likely to be meaningful. Brain structures do not exist in isolation. . . . If the brain as a whole has any one function, it is information processing. . . . Whether or not any given brain "structure" like the hippocampus plays any particular or specialized role . . . it seems very unlikely that a single phrase from the English language, such as "behavioral inhibition" or "spatial map," can serve adequately to characterize its functions.[40]

This suggests that a profitable approach to brain modeling would be to study how the hippocampus interacts with other brain structure to produce behaviors. Such models focus on how information is processed in each region of the brain before being stored or passed on to the next region. This kind of information-processing theory should provide a blueprint for creating a computer program or model to simulate the brain, and this should include recognizable components that perform the functions of the hippocampus and other brain structures. The entire system should show behavior comparable to that of normal animals and humans. When the computer model's "hippocampal region" is damaged, the model should show the same pattern of deficits—and of spared learning—as animals and humans with hippocampal-region damage.

To understand the methods of information-processing theories of brain function in general, and of the hippocampal-region in particular, the next three chapters provide an introduction to the fundamentals of neural network modeling. Chapter 3 serves as an initial introduction to simple neural network models, focusing on the learning rules used for the formation of associations and the application of these rules to understanding the cerebellum. For continuity with the rest of the book, these networks will be illustrated through their application to classical conditioning. Chapter 4 introduces the key issues of stimulus representation—the problem of how to capture within a formal model the events of interest in the natural learning situation, such as the tones, lights, and airpuffs described above. Chapter 5 considers how animals and people learn from mere exposure to stimuli—as in the first phase of the sensory preconditioning task described above—and what kinds of neural networks can capture this type of learning.

Chapter 5 is the last of the tutorial chapters making up part I of this book. Beginning in chapter 6, part II introduces several neural network models of the interactions between the hippocampus and other brain regions during learning.

SUMMARY

• The hippocampal region includes the hippocampus (subfields CA1-CA4), the dentate gyrus, the subiculum, and the entorhinal cortex. The hippocampal region is sometimes defined as including the fimbria/fornix, a fiber pathway that connects the hippocampus to subcortical structures. In humans, the structures of the hippocampal region are located in the medial temporal lobes.

• Most neuroscientists now agree that the hippocampus plays an important role in learning and memory, but there is little consensus as to what that role is.

• Patients such as HM and RB with damage to the medial temporal lobe (hippocampal region) show anterograde amnesia, which is characterized by inability to form new declarative memories—memories such as autobiographical episodes and facts that are easily verbalized. There may be relative sparing of older memories, intelligence, attention, and personality. Anterograde amnesia is often accompanied by some degree of retrograde amnesia, loss of memories formed just before the trauma. Etiologies that can result in anterograde amnesia include stroke, anoxia or hypoxia, herpes encephalitis, normal aging, and Alzheimer's disease, all of which can damage the hippocampus and nearby structures.

• Nondeclarative or procedural learning, such as perceptual learning and motor skill learning, may be spared in amnesia.

• Animal studies have concentrated on developing nonhuman analogs of declarative memory, on identifying tasks such as spatial learning that are especially sensitive to hippocampal damage, and on developing experimental procedures such as classical eyeblink conditioning that are similar across species.

• Eyeblink conditioning is spared after hippocampal lesion, but in the normal brain, the hippocampus does indeed contribute to eyeblink conditioning. Thus, there is a distinction between behaviors for which the hippocampus is needed and those to which it normally contributes.

• The wide range of deficits following hippocampal damage limits the utility of descriptive theories of hippocampal function that focus on a single type of behavior. An alternative approach is to construct information-processing theories of hippocampal function, which attempt to specify how the hippocampus processes information and how the results of this computation are used by other brain regions.