Part VI
Cognitive Neuroscience

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Learning and Memory

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Trapped in the Eternal Now

Henry Molaison, known to the world as “patient H.M.” in a classic series of research articles, was probably the most famous research subject in the history of brain science. Henry started to suffer seizures during adolescence, and by his late 20s, Henry’s epilepsy was out of control. Because tests showed that his seizures began in both temporal lobes, a neurosurgeon removed most of the anterior temporal lobes, on both sides, in 1953.

After Henry recovered from the operation, his seizures were milder, and they could be controlled by medication. But this relief came at a terrible, unforeseen price: Henry had lost the ability to form new memories (Scoville and Milner, 1957). For more than 50 years after the surgery, until his death in 2008, Henry could retain any new fact only briefly; as soon as he was distracted, the newly acquired information vanished. Long after the surgery, he didn’t know his age or the current date, and he didn’t know that his parents (with whom he lived well into adulthood) had died years previously. His IQ remained a little above average (Corkin et al., 1997) because most IQ tests monitor problem solving that doesn’t require remembering new facts for more than a few minutes. Henry knew that something was wrong with him, because he had no memories from the years since his surgery, or even memories from earlier the same day.

Every day is alone in itself, whatever enjoyment I’ve had, and whatever sorrow I’ve had… Right now, I’m wondering, have I done or said anything amiss? You see, at this moment everything looks clear to me, but what happened just before? That’s what worries me. It’s like waking from a dream. I just don’t remember. (B. Milner, 1970, p. 37)

Henry’s inability to form new memories meant that he couldn’t construct a lasting relationship with anybody new. No matter what experiences he might share with someone he met, Henry would have to start the acquaintance anew the following day, because he would have no recollection of ever meeting the person before.

What happened to Henry, and what does his experience teach us about learning and memory?

All the distinctively human aspects of our behavior are learned: the languages we speak, how we dress, the foods we eat and how we eat them, our skills and the ways we reach our goals. So much of our own individuality depends on learning new information and remembering that information to use in the future. As Henry’s case makes clear, conditions that impair memory are particularly frightening; they can make it impossible to build relationships and can rob us of our identity.

Functional Perspectives on Memory

We can discover a great deal about learning and memory by examining how they fail. Clinical case studies show that memory can fail in very different ways, indicating that there are different forms of learning and memory, and that multiple brain regions are involved. The clinical research has guided further studies, employing animal models and brain-imaging technology; together, these diverse approaches are generating a comprehensive picture of brain mechanisms of learning and memory.
There Are Several Kinds of Memory and Learning

The terms learning, the process of acquiring new information, and memory, the ability to store and retrieve that information, are so often paired that it sometimes seems as if one necessarily implies the other. We cannot be sure that learning has occurred unless a memory can be elicited later. Study of different types of memory impairment has revealed different classes of learning and memory, which we will discuss later in the chapter. So let’s start our survey by looking at a few classic case studies of memory impairment.

For patient H.M., the present vanished into oblivion

Patient H.M.—Henry Molaison, whom we met at the start of the chapter—suffered from amnesia (Greek for “forgetfulness”), a severe impairment of memory. In Henry’s case, most old memories remained intact, but he had difficulty recollecting any events after his surgery. Loss of memories formed prior to an event (such as surgery or trauma) is called retrograde amnesia (from the Latin retro-, “backward,” and gradī, “to go”) and is not uncommon. What was striking about Henry was a far more unusual symptom: his apparent inability to retain new material for more than a brief period. The inability to form new memories after an event is called anterograde amnesia (the Latin antero- means “forward”).

Over the very short term, Henry’s memory was normal. If given a series of six or seven digits, he could immediately repeat the list back without error. But if he was given a list of words to study and then tested on them after other tasks had intervened, he could not repeat the list or even recall that there was a list. So Henry’s case provided clear evidence that short-term memory differs from long-term memory—a distinction long recognized by biological psychologists on behavioral grounds (W. James, 1890) and which we will discuss in more depth later.

Henry’s surgery removed the amygdala, most of the hippocampus, and some surrounding cortex from both temporal lobes (FIGURE 17.1). The memory deficit seemed to be caused by loss of the hippocampus, because other surgical patients who had re-
ceived the same type of damage to the amygdala, but less damage to the hippocampus, did not exhibit memory impairment. But to the puzzlement of researchers, it soon became evident that bilateral hippocampal lesions in laboratory animals seemed not to produce widespread memory deficits (Isaacson, 1972). What might account for this discrepancy between humans and lab animals?

An interesting finding about Henry’s memory deficit offered a clue. When Henry was given a mirror-tracing task (FIGURE 17.2A), he improved considerably over ten trials (B. Milner, 1965). The next day the test was presented again. When asked if he remembered it, Henry said no, yet his performance was better than at the start of the first day (FIGURE 17.2B). Over three successive days, Henry never recognized the task, but his improved tracings showed evidence of memory, in the form of motor skill. If an animal subject with comparable brain damage showed similar improvement on a task, we would probably conclude that the animal had normal memory, because we cannot ask rats if they recognize a maze.

So, was Henry’s deficit simply an inability to learn verbal material? Probably not. First, patients like Henry have difficulty reproducing or recognizing pictures and spatial designs that are not recalled in verbal terms. Second, although the patients have difficulty with the specific content of verbal material, they can learn some kinds of information about verbal material (N. J. Cohen and Squire, 1980). For example, several kinds of patients with amnesia can learn the skill of reading mirror-reversed text but show impaired learning of specific words.

Thus, the important distinction is probably not between motor and verbal performances but between two kinds of memory:

1. **Declarative memory** is what we usually think of as memory: facts and information acquired through learning. It is memory we are aware of accessing, which we can declare to others. This is the type of memory so profoundly impaired by Henry’s surgery. Tests of declarative memory take the form of requests for specific information that has been learned previously, such as a story or word list.

2. **Nondeclarative memory**, or procedural memory—that is, memory about perceptual or motor procedures—is shown by performance rather than by conscious recollection. Examples of procedural memory include skilled mirror tracing and mirror reading, as we just described. More familiar uses of procedural memory include skills like bicycling or juggling: things that you learn by doing.

Put another way, declarative memory deals with what, and nondeclarative memory deals with how (summarized in FIGURE 17.3). So, an animal’s inability to speak is probably not what accounts for its apparent immunity to the effects of temporal lesions on memory storage. Rather, the culprit is the difficulty of measuring declarative memory in animals. Later we’ll discuss how to measure declarative memory in animals.
CHAPTER 17

A patient who is unable to encode new declarative memories, because of damage to the dorsal thalamus and the mammillary bodies.

Korsakoff’s syndrome A memory disorder, related to a thiamine deficiency, that is generally associated with chronic alcoholism.

Confabulate To fill in a gap in memory with a falsification; often seen in Korsakoff’s syndrome.

Patient N.A. A patient who is unable to encode new declarative memories, because of damage to the dorsal thalamus and the mammillary bodies.

Patient K.C. A patient who sustained damage to the cortex that renders him unable to form and retrieve new episodic memories, especially autobiographical memories.

Damage to the medial diencephalon can also cause amnesia

The temporal lobe is not the only brain region involved in the formation of declarative memories. For example, the case of patient N.A. indicates that damage to the diencephalon (thalamus and hypothalamus) can also impair memory formation (Squire and Moore, 1979; Teuber et al., 1968). N.A. acquired amnesia as the result of a bizarre accident in which a miniature sword injured his brain after entering through his nostril. N.A. has a striking case of anterograde amnesia, primarily for verbal material, and he can give little information about events since his accident in 1960, but he shows almost normal recall for earlier events (Kaushall et al., 1981).

MRI study of N.A. (FIGURE 17.4) shows damage to several diencephalic structures: clear damage to the left dorsal thalamus, bilateral damage to the mammillary bodies (limbic structures in the hypothalamus), and probable damage to the mammillothalamic tract (Squire et al., 1989). Like Henry Molaison, N.A. shows normal short-term memory but is impaired in forming declarative (but not nondeclarative/procedural) long-term memories. The similarity in symptoms suggests that the medial temporal region damaged in Henry’s brain and the midline diencephalic region damaged in N.A. are normally parts of a larger memory system.

Patients with Korsakoff’s syndrome show damage to medial diencephalic structures and to the frontal cortex

People with Korsakoff’s syndrome—named for its nineteenth-century discoverer, Russian neurologist Sergei Korsakoff—also have anterograde amnesia for declarative memories. People with Korsakoff’s syndrome frequently deny that anything is wrong with them, and they often confabulate—that is, fill a gap in memory with a falsification that they seem to accept as true.

The main cause of Korsakoff’s syndrome is lack of the vitamin thiamine (or B1). Alcoholics who obtain most of their calories from alcohol and neglect their diet often exhibit this deficiency. Treating them with thiamine can prevent further deterioration of memory functions but will not reverse the damage already done.

Temporal lobe structures, including the hippocampus, are typically normal in patients with Korsakoff’s syndrome (Mair et al., 1979). But their brains show shrunken, diseased mammillary bodies, as well as some damage in the dorsomedial thalamus. This damage is similar to that seen in N.A. The mammillary bodies may serve as a processing system connecting medial temporal regions (such as those removed from Henry Molaison) to the thalamus via the mammillothalamic tract and, from there, to other cortical sites (Vann, 2010). Damage to the basal frontal cortex, also found in patients suffering from Korsakoff’s syndrome, probably causes the denial and confabulation that differentiates them from other patients who have amnesia, such as Henry.

Brain damage can destroy autobiographical memories while sparing general memories

One striking case study illustrates an important distinction between two subtypes of declarative memory. Patient K.C., who sustained brain damage in a motorcycle accident at age 30, can no longer retrieve any personal memory of his past, although his general knowledge remains good. He converses easily and plays a good game of chess, but he cannot remember where he learned to play chess or who taught him the game. Detailed autobiographical declarative memory of this sort is known as episodic memory: you
show episodic memory when you recall a specific episode in your life or relate an event to a particular time and place. In contrast, semantic memory is generalized declarative memory, such as knowing the meaning of a word without knowing where or when you learned that word (Tulving, 1972). If care is taken to space out the trials to prevent interference among items, K.C. can acquire new semantic knowledge (Tulving et al., 1991). But even with this method, K.C. cannot acquire new episodic knowledge.

Brain scans of K.C. reveal extensive damage to the cerebral cortex and severe shrinkage of the hippocampus and parahippocampal cortex (Rosenbaum et al., 2005). As with Henry, the bilateral hippocampal damage probably accounts for K.C.’s anterograde declarative amnesia but not for the selective loss of nearly his entire autobiographical memory (i.e., retrograde episodic amnesia), because other patients with restricted hippocampal damage apparently lack this symptom. K.C.’s inability to recall any autobiographical details of his life, even memories from years before his accident, may instead be a consequence of his cortical injuries (Tulving, 1989).

There are a few rare individuals who have incredibly extensive episodic memories, who can tell you what they had for breakfast on June 20, 2009, or any other date (Price, 2008). A group of 11 such people with extreme autobiographical memory were found to have larger temporal lobes, including a larger parahippocampal gyrus, than controls (LePort et al., 2012). We do not know whether these people were born with larger temporal lobes, and so had great autobiographical memory, or developed great autobiographical memory, which caused their temporal lobes to enlarge.

**Different forms of nondeclarative memory serve varying functions**

We have seen that there are two different kinds of declarative memory: semantic and episodic. There are several different types of nondeclarative memory too.

In skill learning, subjects perform a challenging task on repeated trials in one or more sessions. The mirror-tracing task performed by Henry Molaison (see Figure 17.2) is an example. Learning to read mirror-reversed text, also mentioned earlier, is a type of perceptual skill learning.

Priming, also called repetition priming, is a change in the processing of a stimulus, usually a word or a picture, as a result of prior exposure to the same stimulus or related stimuli. For example, if a person is shown the word *stamp* in a list and later is asked to complete the word stem *STA-* , he or she is more likely to reply “stamp” than is a person who was not exposed to that word. Even patients like Henry, who do not recall being shown the list of words, nevertheless show the effect of priming.

Conditioning is learning simple associations between stimuli. Different brain areas are responsible for conditioning, depending on the kind of conditioning, as we’ll discuss later.

The taxonomy of memory we presented in Figure 17.3 is updated in **FIGURE 17.5**, where we have added the subtypes of declarative and nondeclarative memory described in this section, along with some examples.
Memory Has Temporal Stages: Short, Intermediate, and Long

The span of time that a piece of information will be retained in the brain varies. Although investigators often contrast short-term and long-term memories, this dichotomy is an oversimplification. Evidence suggests at least four different duration categories for memory. The briefest memories are called **iconic memories** (from the Greek *eikon*, “image”); an example is the fleeting impression of a glimpse scene that vanishes from memory seconds later. These brief memories are thought to be residual sensory neural activity—the so-called sensory buffers (FIGURE 17.6).

Somewhat longer than iconic memories are **short-term memories (STMs)**. If you look up a phone number and keep it in mind (perhaps through rehearsal) just until you make the phone call, you are using STM. In the absence of rehearsal, STMs last only about 30 seconds (J. Brown, 1958; L. R. Peterson and Peterson, 1959). With rehearsal, you may be able to retain an STM until you turn to a new task a few minutes later, but when the STM is gone, it’s gone for good. Many researchers now refer to this form of memory as **working memory**, in recognition of the way we use it; this is where we hold information while we are working with it to solve a problem or are otherwise actively manipulating the information. One influential model (Baddeley, 2003) subdivides working memory into three complementary components:

1. A **phonological loop** that contains auditory information (such as speech); this is what you use to rehearse that phone number.
2. A so-called **visuospatial sketch pad** that holds visual impressions of stimuli; you use this to imagine the route back to your car in a parking building.
3. An **episodic buffer** that contains more-integrated information, spanning across sensory modalities, sort of like movie clips.

According to this model, the flow of information into and out of working memory is supervised by a fourth module, an **executive control**, which we’ll discuss in Chapter 18.

Some memories last only a little longer than short-term memories. Chances are good that you can remember what you had for lunch today or yesterday, but not most of your lunches last week. You may recall today’s weather forecast, but not that of a few days ago. These are examples of what some (but not all) memory researchers identify as **intermediate-term memory** —that is, a memory that outlasts STM but is far from being permanent (M. R. Rosenzweig et al., 1993).

The really long-lasting memories—the address of your childhood home, how to ride a bike, your first love—are called **long-term memories (LTMs)**, lasting from days to years. A substantial body of evidence indicates that STM and LTM, in particular, rely on different processes to store information. A classic demonstration involves learning lists of words or numbers. If you hear a series of ten words and then try to repeat them back after a 30-second delay, you will probably do especially well with the earliest few words, which is termed a **primacy effect**; you will also do well with the last few words, termed a **recency effect**, and less well with words in the middle of the list. FIGURE 17.7 shows typical results from such an experiment: a U-shaped **serial position curve**. If the delay prior to recall is a few minutes instead of a few seconds, there is no recency effect; the recency effect is short-lived and thus attributed to working memory (or STM). The primacy effect, however, lasts longer and is usually attributed to LTM. Like humans, various experimental animals show U-shaped serial position functions (A. A. Wright et al., 1985)—a finding that confirms the basic distinction between working memory and LTM.

Similarly, patients with amnesia caused by impairment of the hippocampus show a reduced primacy effect but retain the recency effect (see Figure 17.7)—their STM is intact. Pharmacological manipulations also reveal the different stages of memory, as reviewed in *A Step Further: Memories of Different Durations Form by Different Neurochemical Mechanisms* on the website.
Long-term memory is vast

You might think it would be wonderful to effortlessly recall almost everything from your past, but studies of real-life cases reveal that perfect recall—for example, being able to remember in detail what you did on a specific date for each of the last 10 years—is a great burden. Without the usual process of pruning out unimportant memories, continual perfect recall can become uncontrollable, distracting, and exhausting (Luria, 1987; Parker et al., 2006). These cases also illustrate that the brain’s memory systems—even the more fallible versions found in most of us—have the capability to retain vast amounts of information. We take this capacity for granted and barely notice, for example, that knowledge of a language involves remembering at least 100,000 pieces of information. Most of us also store a huge assortment of information about faces, tunes, odors, skills, stories, and so on.

Our memories are acquired rapidly and retained well. In one classic experiment, subjects viewed long sequences of color photos of various scenes; several days later, the subjects were shown pairs of images—in each case a new image plus one from the previous session—and asked to identify the images seen previously. Astonishingly, subjects performed with a high degree of accuracy for series of up to 10,000 different stimuli, prompting the researcher to conclude that for all practical purposes, “there is no upper bound to memory capacity” (Standing, 1973). Similar impressive feats of memory in our distant relatives, such as pigeons (Vaughan and Greene, 1984), illustrate that a great capacity for information storage is a general property of nervous systems across the animal kingdom.

17.7 Serial Position Curves from Immediate-Recall Experiments

(A) These curves show the percentage of correct responses for immediate recall of a list of ten words. The patients with amnesia (blue curve) performed as well on the most recent items (8–10) as the control group did, but they performed significantly worse on earlier items. (B) Testing immediately after presenting the list prevents the primacy effect, while long delays between presentation and testing block the recency effect, as those last few items are no longer in short-term memory. (After Baddeley and Warrington, 1970.)
Despite the vast capacity of LTM, we all normally forget information, or we have inaccurate recollections. The discomfort felt by those rare people with perfect recall shows us that forgetting is a normal aspect of memory, helping to filter out unimportant information and freeing up needed cognitive resources (Kuhl et al., 2007). Interestingly, memories don’t simply deteriorate from disuse and the passage of time; instead, they tend to suffer interference from events before or after their formation, as we’ll see later.

**Successive Processes Capture, Store, and Retrieve Information in the Brain**

A functional memory system must incorporate three aspects of information processing: (1) **encoding** of raw information from sensory channels into short-term memory, (2) **consolidation** of the volatile short-term traces into more-durable long-term memory, and (3) eventual **retrieval** of the stored information for use in future behavior (Fig. 17.8). A problem with any of these processes can cause us to forget information.

**Multiple brain regions are involved in encoding**

A special “event-related” fMRI procedure has been used to study the encoding process (Rosen et al., 1998). First the brain was repeatedly and rapidly scanned while a series of stimulus items was presented. Then the fMRI activations elicited by individual items were classified according to whether subjects successfully recognized them later (indicating that successful encoding must have occurred) or failed to recognize them (no encoding). The analysis showed that although the stimuli activated many brain areas, only a few brain areas predicted which stimuli would later be recognized. When the stimuli were pictures (Brewer et al., 1998), the critical areas showing greater activation to correctly recalled stimuli were the right prefrontal cortex and the parahippocampal cortex in both hemispheres. In the case of words (A. D. Wagner et al., 1998), the critical areas were the left prefrontal cortex and the left parahippocampal cortex. These results indicate that parahippocampal and prefrontal cortex are crucial for consolidation, and these mechanisms reflect the hemispheric specializations (left hemisphere for language and right hemisphere for spatial ability) that we’ll discuss in Chapter 19.
Different mechanisms are used for consolidating and retrieving declarative information

Studies of patients with brain injuries, like Henry Molaison, indicate that consolidation of declarative long-term memories involves the hippocampus (M. Lepage et al., 1998). But where are the new long-term memories actually being stored? Because Henry could recall events before his surgery, those memories must have been stored somewhere other than the hippocampus. We refer to the physical changes in the brain that underlie a long-term memory as an **engram** (from German, “to put in writing”). The physical basis of a memory is also sometimes called a **memory trace**, recognizing that the memory is likely to be due to changes in several different synapses within some neural circuit, as we’ll discuss later.

In laboratory studies investigating this question, animals received lesions of the hippocampal formation at various intervals after learning trials (J. J. Kim and Fanselow, 1992; Winocur, 1990; Zola-Morgan and Squire, 1990). In general the surgery impaired memory for items learned most recently before the surgery. Material learned a bit earlier was unaffected. These results confirm that the hippocampus cannot be the repository of engrams. Instead, although the hippocampus is important over the shorter term for consolidation of a memory, after that period the memory is stored in the cortex. An important principle that has emerged from this area of research is that permanent storage of information tends to be in the regions of the cortex where the information was first processed and held in short-term memory. For example, visual cortex is crucial for visual object recognition memory (López-Aranda et al., 2009). After further processing that involves the medial temporal region, the permanent memory storage becomes independent and memories can be retrieved directly for use by other cognitive processes. This schema is illustrated in **FIGURE 17.9**.

**FIGURE 17.9 Encoding, Consolidation, and Retrieval of Declarative Memories**  (A) According to this model, medial temporal lobe processes distribute the various sensory attributes of an event, and linkages between them, in corresponding regions of cortex. (B) Before consolidation is complete, retrieval involves the hippocampus and other medial temporal structures. (C) After consolidation, retrieval may occur independent of the medial temporal system.
Emotions and Memory

Almost everyone knows from personal experience that strong emotions can potently enhance memory formation and retrieval. Examples of memories enhanced in this way might include a strong association between special music and a first kiss, or uncomfortably vivid recollection of the morning of September 11, 2001. Interestingly, our memories about learning of such events, which seem so vivid and detailed, are not nearly as accurate as they seem (Hirst et al., 2009). Nevertheless, people who actually experience life-threatening events often develop posttraumatic stress disorder (PTSD), characterized as “reliving experiences such as intrusive thoughts, nightmares, dissociative flashbacks to elements of the original traumatic event, and...preoccupation with that event” (Keane, 1998, p. 398). For these people, whether the details of their memories are accurate is irrelevant because their suffering is certainly real.

In animal models, stress and emotional arousal do enhance memory, and a suite of transmitters are involved, including the opioids, GABA (gamma-aminobutyric acid), and especially the adrenergic transmitters epinephrine (adrenaline) and norepinephrine (NE). Epinephrine (adrenaline), released by the adrenal

Not all memories are created equal. We all know from firsthand experience that emotion can powerfully enhance our memory for past events. For example, an emotionally arousing story is remembered significantly better than a closely matched but emotionally neutral story (Reisberg and Heuer, 1995). But if people are treated with propranolol (a beta-adrenergic antagonist, or “beta-blocker,” that blocks the effects of epinephrine), this emotional enhancement of memory vanishes. It’s not that treated subjects perceive the story as being any less emotional; in fact, treated subjects rate the emotional content of the stories just the same as untreated subjects do. Instead, the evidence indicates that propranolol directly interferes with the ability of adrenal stress hormones to act on the brain (Cahill et al., 1994), as discussed in BOX 17.1.

Retrieving memories can strengthen them, or distort them

The process of retrieving information from LTM seems to make the memories temporarily unstable and susceptible to disruption or alteration before undergoing reconsolidation and returning to stable status (Nader and Hardt, 2009). It thus seems that using memories makes them plastic again and amenable to updating (Debiec et al., 2002; Eisenberg et al., 2003). On the one hand, if care is taken to be sure the information retrieved is accurate, reconsolidation can be used to strengthen memories you want to keep. One of the best ways to improve learning is simply repeated retrieval (and thus, repeated reconsolidation) of the stored information (Karpicke and Blunt, 2011), taking care that you’re remembering correctly (for example, by turning over the flash card to check your answer). For your next exam, try making up some practice tests for yourself, or have a friend quiz you, instead of simply “cramming.”

But reconsolidation also has the potential to distort memories. For example, each time a memory trace is activated during recall, it is subject to changes and fluctuations, so with successive activations it may deviate more and more from its original form. Furthermore, new information that is provided at the time of recall can add new aspects to the memory trace, so evoking the memory later is likely to reactivate the newer traces along with the older, and to produce distorted memories (Estes, 1997; Nader and Hardt, 2009).

reconsolidation The return of a memory trace to stable long-term storage after it has been temporarily made volatile during the process of recall.

BOX 17.1

The amygdala and memory The diagram shows sites of activity of drugs that affect different neuromodulatory and neurotransmitter systems in the amygdala. ACh, acetylcholine; GABA, gamma-aminobutyric acid; NE, norepinephrine; OP, opioids. (After McGaugh, 2003.)
This is why people sometimes “remember” events that never happened. We can create false memories by asking leading questions—“Did you see the broken headlight?” rather than “Was the headlight broken?”—or by providing misinformation via trusted channels (Loftus, 2003). For example, by burying false details in a biography provided to some subjects, researchers found it relatively easy to plant a childhood memory of meeting a Bugs Bunny character at a Disney resort (Braun et al., 2002)—something that could never happen in real life (because Bugs is a Warner Bros. character).

This possibility of planting false memories clouds the issue of “recovered memories” of childhood sexual or physical abuse. Controversial therapeutic methods such as hypnosis or “guided imagery” (in which the patient is encouraged to imagine hypothetical abuse scenarios) can inadvertently plant false details during reconsolidation (Figure 17.10). Indeed, one study found that people who had “recovered” memories of childhood sexual abuse were more easily manipulated into falsely remembering a word, when brought to the laboratory and asked to remember lists of words, than were control subjects or people who had always remembered their childhood abuse (McNally, 2003).

For example, if people who have just had a traumatic experience are given the beta-adrenergic antagonist propranolol, which blocks the effects of epinephrine, their memory for the event is significantly reduced when tested months later (Pitman et al., 2002).

In PTSD, each recurrence of the strong emotions and memories of the traumatic event may reactivate memories that, when reconsolidated in the presence of stress signals like epinephrine, become even stronger. Therefore, one strategy to treat PTSD could be to block the effects of epinephrine while the person is retrieving the traumatic memory, to blunt the emotional experience of the event and thereby weaken that aspect of the memory during reconsolidation. A study with rats found that when a previously formed fear memory is reactivated, it can be weakened by administration of propranolol up to 2 hours after reactivation of the memory (Przybyslawski et al., 1999; Sara, 2000). In a trial of people suffering from PTSD, having them read aloud a written description of their ordeal while under the influence of propranolol reduced their symptoms (A. Brunet et al., 2011) such that most no longer met the diagnostic criteria for PTSD. They still remembered the details of the event, but they no longer found the memory so upsetting. If we cannot erase the traumatic memory altogether, perhaps we can reduce its sting.

**posttraumatic stress disorder (PTSD)** A disorder in which memories of an unpleasant episode repeatedly plague the victim.
A test in which the subject must respond to the unfamiliar stimulus of a pair.

Different Brain Regions Process Different Aspects of Memory

In this section we will first consider the roles of different parts of the medial temporal lobe in the formation of declarative memory, and then we'll take up how other parts of the brain are involved in the formation of memories for specific aspects of experience.

Medial temporal lobe structures are crucial for declarative memory

Publication of Henry Molaison’s case prompted an intensive effort to develop methods for systematically studying declarative memory in monkeys and other lab animals because, as we wrote earlier, animals cannot speak to tell us what they remember. To get around this problem, the delayed non-matching-to-sample task (FIGURE 17.11)—a test of object recognition memory—was developed. In this task, monkeys must identify which of two objects was not seen previously, with delays ranging from 8 seconds to 2 minutes (Spiegler and Mishkin, 1981). The important feature of this procedure is that the animal does not reach for the item that previously had a treat under it, because in that case the monkey might unconsciously associate reward with that object even if the animal had no conscious recollection of it. Instead, the monkey declares that it remembers the object by reaching for the other object, the one that was not associated with a reward previously. Monkeys with extensive damage to the medial temporal lobe, and thus similar to Henry, are severely impaired on this task, especially with the longer delays. But which specific temporal lobe structures are most important?

Selective removal of specific parts of the medial temporal lobes of monkeys revealed that the amygdala—one of the structures removed in Henry’s surgery—was not crucial for performance on tests of declarative memory. However, removal of the adjacent hippocampus significantly impaired performance on these tests and, as shown in FIGURE 17.12, the deficit was even more pronounced when the hippocampal damage was paired with lesions of the nearby entorhinal and parahippocampal cortex, and much worse when lesions of perirhinal cortex were added (Zola-Morgan et al., 1994). Human patients similarly show larger impairments when both the hippocampus and medial temporal cortex are damaged (Rempel-Clower et al., 1996; Zola-Morgan and Squire, 1986).

Overall, the performance of experimental animals suggests that the hippocampus acts as the final stage of convergence for adjacent regions of cortex (Zola et al., 2000; Squire et al., 2007), resulting in storage of declarative memories in the cortex.

Imaging studies have revealed much about declarative memory

As expected from the studies of patients with amnesia and of lesioned lab animals already discussed, brain-imaging studies confirm the crucial importance of medial temporal (hippocampal) and diencephalic systems in forming long-term memories.
These regions are activated during both encoding of new material and retrieval (Schacter et al., 1996; Tulving et al., 1996). But as we mentioned earlier, long-term storage appears to depend on the cortex.

Some patients with lesions of the cortex seem to lose their memory of specific categories of objects, such as animals, names of different tools, or brands of automobiles. Neuroimaging studies of normal subjects are consistent with the observations in people with cortical damage. For example, asking subjects to name tools or animals activates cortical regions that overlap in some areas but differ in others (A. Martin et al., 1996).

Brain imaging has also been used to study the distinction between semantic (general) memory and episodic (autobiographical) memory, exemplified by patient K.C., in normal subjects. In one study, subjects listened to autobiographical passages and to passages written by other people (G. R. Fink et al., 1996). The autobiographical passages, relative to the others, caused greater activation of right frontal and temporal lobe regions, as FIGURE 17.13 shows. Thus, autobiographical memories and semantic memories appear to be processed in different locations.

17.12 Memory Performance after Medial Temporal Lobe Lesions (A) In this ventral view of a monkey brain, the hippocampus is embedded beneath (dorsal to) the entorhinal cortex (orange) and perirhinal cortex (yellow). The parahippocampal cortex is shown in green. (B) Different bilateral lesions of the medial temporal lobe yielded different results in tests of memory. (After Squire and Zola-Morgan, 1991.)

17.13 My Story versus Your Story Autobiographical passages (A) cause greater activation of the right frontal and temporal lobes than do nonautobiographical passages (B). (After G. R. Fink et al., 1996, courtesy of Gereon Fink.)

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Hippocampal mechanisms are important in spatial memory

The caricature of the white-coated biopsychologist watching rats run in mazes, a staple of cartoonists to this day (FIGURE 17.14), has its origins in the intensive memory research of the early twentieth century. The early work indicated that rats and other animals don’t just learn a series of turns but instead form a cognitive map (an understanding of the relative spatial organization of objects and information) in order to solve a maze (Tolman, 1949). Animals apparently learn at least some of these details of their spatial environment simply by moving through it—an example of latent learning (Tolman and Honzik, 1930).

We now know that, in parallel with its role in other types of declarative memory, the hippocampus is a crucial neural participant in spatial learning. Within the rat hippocampus are found many neurons that selectively encode spatial location (O’Keefe and Dostrovsky, 1971; Leutgeb et al., 2005). These place cells become active when the animal is in—or moving toward—a particular location. If placed in a new environment, place cell activity indicates that the hippocampus remaps to the new locations (Moita et al., 2004). Lesions of this part of the hippocampus severely impair spatial learning in rats (McNaughton et al., 1996) and humans (Bartsch et al., 2010).

Two types of cells discovered in nearby entorhinal cortex probably help the animal to learn the local spatial environment. Grid cells fire selectively when the animal crosses the intersection points of an abstract grid map of the local environment, acting like an innate system of latitude and longitude (Hafting et al., 2005). Such cells have also been identified in humans (Doeller et al., 2010). Arrival at the perimeter of the local spatial map is signaled by the activation of entorhinal border cells (Solstad et al., 2008).

**SPATIAL MEMORY AND THE EVOLUTION OF HIPPOCAMPAL SIZE**

Careful comparisons of natural behavior and brain anatomy have revealed that for many species, their manner of making a living has left an imprint on the hippocampus. For example, not only does the monkey hippocampus contain place cells (Rolls and O’Mara, 1995), it also features spatial view cells that respond to the part of the environment that the monkey is looking at, perhaps reflecting the importance of vision for primates.

As another example, species of birds that hide caches of food in spatially scattered locations have larger hippocampi than noncaching species, even when the comparison species are very close relatives that have otherwise similar lifestyles (Krebs et al., 1989; Sherry, 1992; Sherry et al., 1989) (see Figure 6.6). Lesions of the hippocampus impair the ability of these birds to store and retrieve caches of food (Sherry and Vaccarino, 1989). Homing pigeons also have enlarged hippocampi relative to other varieties of pigeons, presumably serving the spatial demands of their prodigious navigational abilities (Rehkamper et al., 1988). A relationship between spatial cognition and hippocampal size is evident in mammals too. Just as with the food-caching birds, Merriam’s kangaroo rat, which stashes food in scattered locations, has a significantly larger hippocampus than its noncaching cousin, the bannertail kangaroo rat (L. F. Jacobs and Spencer, 1994).

In voles, mating strategies and sex differences in spatial behavior, rather than food caching, seem to have shaped the hippocampus. In nature, pine voles and prairie voles are monogamous, and males and females have comparably sized home ranges. But their close relatives, the meadow voles, are polygynous, so meadow vole males’ home ranges are much larger and encompass the home ranges of several females. In meadow voles, but not in pine voles, males have larger hippocampi than females (L. F. Jacobs et al., 1990), reflecting this sex-related species difference in spatial processing (FIGURE 17.15). Accordingly, when studied in the laboratory, a significant male-favoring sex difference in spatial ability is found only for the meadow voles (Gaulin and Fitzgerald, 1989). Even within individual life spans, spatial learning can change the anatomy of the hippocampus. For a fascinating example in humans, see A Step Further: Mastering London Topography Changes Hippocampal Structure in Taxi Drivers on the website.

cognitive map  A mental representation of a spatial relationship.
latent learning  Learning that has taken place but has not (yet) been demonstrated by performance.
place cell  A neuron within the hippocampus that selectively fires when the animal is in a particular location.
grid cell  A neuron that selectively fires when the animal crosses the intersection points of an abstract grid map of the local environment.
border cell  A neuron that selectively fires when the animal arrives at the perimeter of the local spatial cognitive map.
Imaging studies help us understand nondeclarative memory

As noted earlier, three major categories of nondeclarative (procedural) memory are skill learning, repetition priming, and conditioning. Each of these types of nondeclarative memory has been investigated with modern functional-imaging technology.

**SKILL MEMORY**  Imaging studies have investigated learning and memory for different kinds of skills, including sensorimotor skills (e.g., mirror tracing; see Figure 17.2), perceptual skills (e.g., learning to read mirror-reversed text), and cognitive skills (tasks involving planning and problem solving, common in puzzles like the Tower of Hanoi problem, which you can play on the website). All three kinds of skill learning are impaired in people with damage to the basal ganglia; damage to other brain regions, especially the motor cortex and cerebellum, also affects aspects of some skills.

Neuroimaging studies confirm that the basal ganglia, cerebellum, and motor cortex are important for sensorimotor skill learning in normal people (Grafton et al., 1992). For example, learning specific sequences of finger movements is associated with selective activation of motor cortex and the basal ganglia (Doyon et al., 1996; Hazeltine et al., 1997), with the cerebellum possibly providing error correction during learning (Flament et al., 1996). Often the activations shift among brain regions as performance changes during the course of learning, so learning appears to involve a complex set of interacting neural networks.

**REPETITION PRIMING**  We mentioned earlier that priming is a change in the processing of a stimulus due to prior exposure to the same or a related stimulus. Priming does not require declarative memory of the stimulus—Henry Molaison and other patients with amnesia have shown priming for words they haven’t remember seeing. In contrast to skill learning, tests show that priming is not impaired by damage to the basal ganglia.

In functional-imaging studies, perceptual priming (priming based on the visual form of words) is related to reduced activity in bilateral occipitotemporal cortex (Schacter et al., 1996), presumably because the priming makes the tasks easier. Conceptual priming (priming based on word meaning) is associated with reduced activation of the left frontal cortex (Blaxton et al., 1996; Gabrieli et al., 1996; A. D. Wagner et al., 1997).

**CONDITIONING**  Experimental evidence in lab animals, which we will discuss later in the chapter, shows that cerebellar circuits are crucial for simple eye-blink conditioning, in which a tone or other stimulus is associated with eye blinking in response to a puff of air. A PET study of human eye-blink conditioning (Logan and Grafton, 1995) found that in the course of conditioning, there was a progressive increase in activity in several regions of the brain, including not only the cerebellum, but also the hippocampus, the ventral striatum, and regions of the cerebral cortex. But activity in these other areas may not be essential for eye-blink conditioning in the way that the cerebellum is. For example, patients with hippocampal lesions can acquire the conditioned eye-blink response, but patients with unilateral cerebellar damage can acquire a conditioned eye-blink response only on the side where the cerebellum is intact (Papka et al., 1994).

**17.15 Sex, Memory, and Hippocampal Size**  Males and females of two species of voles were compared on three variables: (A) size of home range, (B) score on a spatial learning task, and (C) hippocampal size divided by brain size. (After L. F. Jacobs et al., 1990.)
Tests of Specific Attributes of Memory  Brain lesion experiments testing spatial-location recognition (A), response recognition (B), and object recognition (C)—using the setups shown on the left—yielded the results shown on the right. (After Kesner et al., 1993.)

A variety of brain regions are involved in different attributes of working memory

Because they span verbal and nonverbal material, in multiple sensory modalities, for multiple purposes, working memories tend to have unique features or attributes. So, for example, an individual memory may include a mix of information about space, time, sensory perception, response, and/or emotional factors. Researchers have attempted to devise memory tasks that selectively tap some of these attributes of memory, in order to assess the relative contributions of different regions of the brain.
**FIGURE 17.16** presents some examples of tests used to probe working memory (Kesner, 1998; Kesner et al., 1993). For testing *spatial* location memory, the well-known eight-arm radial maze was used (**FIGURE 17.16A**). To solve this task correctly and receive a food reward, rats must recognize and enter an arm of the maze that they have been down shortly beforehand. Rats were tested following surgical lesions of the hippocampus, the caudate nucleus, or the extrastriate cortex (visual cortex outside the primary visual area). Only the animals with hippocampal lesions were impaired on this predominantly spatial task—a result that is consistent with the role of the hippocampus in spatial cognition that we discussed earlier. The test shown in **FIGURE 17.16B** was used to assess the memory of the same rats for their own *motor* behavior. Here the animal must use working memory to remember whether it made a left or right turn a few moments previously, and it receives a food reward only if it makes a turn in the same direction on a follow-up trial. Only the animals with lesions of the caudate nucleus were significantly impaired on this task. Finally, in the test depicted in **FIGURE 17.16C**, the rats were required to hold in working memory the *sensory* attributes of presented stimuli, identifying the novel stimulus in each pair of stimuli presented. Here, only the rats with extrastriate lesions were significantly impaired. This impressive lack of overlap between the symptoms of the different lesions nicely illustrates how memories involving different attributes are parceled out to diverse brain regions for storage.

It’s perhaps not surprising that the brain regions that do the initial processing of the stimuli often also act as the memory buffers for holding the stimuli in working memory—visual information in visual cortex, motor information in motor areas, and so on. One additional common attribute of working memory is the passage of time—a delay between stimulus and response during which information must be held ready for further processing. Delayed-response tasks, which tap this aspect of working memory by varying the delay between the presentation and removal of a stimulus and the response, are especially associated with activity of the prefrontal cortex—particularly the dorsolateral parts—in humans and experimental animals (Funahashi, 2006; H. C. Leung et al., 2002, 2005).

**Brain regions involved in learning and memory: An interim summary**

**FIGURE 17.17** updates and summarizes the taxonomy of long-term memory that we have been discussing. Several major conclusions should be apparent by now, especially (1) that many regions of the brain are involved in learning and memory; (2) that different forms of memory rely on at least partly different brain mechanisms, which may include several different regions of the brain; and (3) that the same brain structure can be a part of the circuitry for several different forms of learning.

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**TABLE 17.1**

<table>
<thead>
<tr>
<th>Brain regions involved</th>
<th>Long-term memory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Declarative</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Episodic</strong></td>
<td>Storage in cortex, perhaps especially in right frontal and temporal regions</td>
</tr>
<tr>
<td><strong>Semantic</strong></td>
<td>Storage in cortex, perhaps especially in temporal lobes</td>
</tr>
<tr>
<td><strong>Skill learning</strong></td>
<td>Basal ganglia, motor cortex, cerebellum</td>
</tr>
<tr>
<td><strong>Nondeclarative (procedural)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Priming</strong></td>
<td>Reduces activity in bilateral occipito-temporal cortex</td>
</tr>
<tr>
<td><strong>Perceptual</strong></td>
<td>Reduces activity in left frontal cortex</td>
</tr>
<tr>
<td><strong>Conceptual</strong></td>
<td>Cerebellar circuit</td>
</tr>
<tr>
<td><strong>Simple conditioning</strong></td>
<td>Hippocampus and cortex</td>
</tr>
<tr>
<td><strong>Complex conditioning</strong></td>
<td></td>
</tr>
</tbody>
</table>
Neural Mechanisms of Memory Storage

What are the basic molecular, synaptic, and cellular events that store information in the nervous system? The remainder of this chapter concerns the cellular and physiological underpinnings of memory, what is called the *engram* or *memory trace*. We will look at some of the ways in which new learning involves changes in the strength of existing synapses, and the biochemical signals that may produce those changes. We’ll consider how the formation of memories may require the formation of new synapses, or even the birth of new neurons. The observation that neuroplasticity (or neural plasticity)—the ability of neurons and neural circuits to be remodeled by events—is found in virtually all animals indicates that it is an ancient and vital product of evolution.

Memory Storage Requires Neuronal Remodeling

In introducing the term *synapse*, Charles Sherrington (1897) speculated that synaptic alterations might be the basis of learning, anticipating an area of research that to this day is one of the most intensive efforts in all of neuroscience. Most current theories of the cellular basis of learning focus on plasticity of the structure and physiological functioning of synapses.

**Plastic changes at synapses can be physiological or structural**

Synaptic changes that may store information can be measured physiologically. The changes could be presynaptic, postsynaptic, or both (Figure 17.18A). Such changes include greater release of neurotransmitter molecules and/or greater effects because the receptor molecules become more numerous or more sensitive. The result of such changes would be an increase in the size of the postsynaptic potential. Changes in the rate of inactivation of the transmitter (through reuptake or enzymatic degradation) could produce a similar effect.

Synaptic activity could also be modulated by inputs from other neurons (members of the same or other cell assemblies) causing extra depolarization or hyperpolarization of the axon terminals and changes in the amount of neurotransmitter released (Figure 17.18B).

Long-term memories may require changes in the nervous system so substantial that they can be directly observed (with the aid of a microscope, of course). Structural changes resulting from use are apparent in other parts of the body. For example, exercise changes the mass and/or shape of muscles and bones. In a similar way, new synapses could form or synapses could be eliminated as a function of training (Figure 17.18C). Training could also lead to reorganization of synaptic connections. For example, it could cause a more used pathway to take over sites formerly occupied by a less active competitor (Figure 17.18D).

There is growing evidence that glia also play a role in learning and synaptic activity. For example, in some systems, nearby astrocytes mark which synapses will change in strength; blocking astrocyte activity prevents the synapse from changing (Min and Nevian, 2012). Also, people learning a new skill show changes in white matter that indicate changes in myelination from oligodendrocytes (Zatorre et al., 2012).

**Varied experiences and learning cause the brain to change and grow**

The remarkable plasticity of the brain is not all that difficult to demonstrate. Simply living in a complex environment, with its many opportunities for new learning, produces pronounced biochemical and anatomical changes in the brains of rats (E. L. Bennett et al., 1964, 1969; Renner and Rosenzweig, 1987; M. R. Rosenzweig, 1984; M. R. Rosenzweig et al., 1961). This area of research is covered in more detail in A Step Further: Cerebral Changes Result from Training on the website.
17.18 Synaptic Changes That May Store Memories  After training, each action potential in the relevant neural circuit causes increased release of transmitter molecules (red dots). The postsynaptic potential (PSP) therefore increases in size, as indicated by the graphs in (A) and (B). (A) Several different changes in the synapse each result in an increase in size of the PSP. (B) An interneuron modulates polarization of the axon terminal and causes the release of more transmitter molecules per nerve impulse. (C) A neural circuit that is used more often increases the number of synaptic contacts. (D) A more frequently used neural pathway takes over synaptic sites formerly occupied by a less active competitor.
In standard studies of environmental enrichment, rats are randomly assigned to three housing conditions:

1. **Standard condition (SC)**  Animals are housed in small groups in standard lab cages (FIGURE 17.19A). This is the typical environment for laboratory animals.

2. **Impoverished condition (IC)**  Animals are housed individually in standard lab cages (FIGURE 17.19B).

3. **Enriched condition (EC)**  Animals are housed in large social groups in special cages containing various toys and other interesting features (FIGURE 17.19C). This condition provides enhanced opportunities for learning perceptual and motor skills, social learning, and so on.

In dozens of studies over several decades, a variety of plastic changes in the brain have been linked to such environmental enrichment. For example, compared with IC animals (or SC animals in many cases), EC animals have heavier, thicker cortex (M. C. Diamond, 1967; M. R. Rosenzweig et al., 1962), with enhanced cholinergic activity (M. R. Rosenzweig et al., 1961). Cortical neurons in EC animals also have more dendritic branches, especially on dendrites closer to the cell body (called basal dendrites), than those from IC animals (Globus et al., 1973; Greenough, 1976) (FIGURE 17.20).

Rats are not the only animals to benefit from environmental enrichment. Similar effects on brain processes and behavior are seen in fishes, birds, mice, cats, and monkeys (Renner and Rosenzweig, 1987; van Praag et al., 2000; Mohammed, 2001). And the evidence indicates that the human brain is no exception: for example, we saw in Chapter 11 that the hand area of the motor cortex becomes larger in musicians, presumably because of their extensive practice. In another example, 100 children assigned to a 2-year enriched nursery school program showed improvements in tests of orienting and arousal when reassessed at age 11 (Raine et al., 2001). And as we will see later in...
this chapter, enriched experience also appears to protect against age-related declines in memory, both in laboratory animals and in humans. However, it is difficult to find the exact synaptic changes that underlie a particular instance of learning, because there are so many synapses (Merchán-Pérez et al., 2009). Researchers made progress by studying simple learning in simple animals, as we discuss next.

Invertebrate Nervous Systems Show Plasticity

One fruitful research strategy has been to focus on memory mechanisms in the very simple nervous systems of certain invertebrates. Invertebrate nervous systems have relatively few neurons (on the order of hundreds to tens of thousands). Because these neurons are arranged identically in different individuals, it is possible to construct detailed neural circuit diagrams for particular behaviors and study the same few neurons in multiple individuals.

An especially successful program of research focused on the sea slug *Aplysia* (Kandel, 2009), a species of animals with a compact nervous system that are nonetheless capable of the simplest type of learning: nonassociative learning. In each of the three forms of nonassociative learning—habituation, dishabituation, and sensitization—a single stimulus is presented once or repeatedly. Habituation is a decrease in response to a stimulus as the stimulus is repeated (when the decrement cannot be attributed to sensory adaptation or motor fatigue). Sitting in a café, you may stop noticing the door chime when someone enters; in this case you have habituated to the chime. Once habituation has occurred, a strong stimulus (of the same sort, or even in another sensory modality) will often cause the response to the habituated stimulus to increase sharply; it may become even larger than the original response. The increase in response amplitude is called dishabituation. So, if a loud firecracker is set off behind

**nonassociative learning**  A type of learning in which presentation of a particular stimulus alters the strength or probability of a response according to the strength and temporal spacing of that stimulus; includes habituation and sensitization.

**habituation**  A form of nonassociative learning in which an organism becomes less responsive following repeated presentations of a stimulus.

**dishabituation**  The restoration of response amplitude following habituation.
17.21 The Sea Slug Aplysia  In the usual posture, the siphon is extended and the gill is spread out on the back. Ordinarily only the tip of the siphon would be visible in a lateral view; here, the rest of the siphon and the gill are shown as if the animal were transparent.

(A) Short-term habituation

When the siphon is first stimulated by a squirt of water, Aplysia retracts its gill, protecting the gill in case the animal is under attack. This reflex is mediated by the sensory neurons synapsing directly upon the motoneurons that withdraw the gill. There are many sensory neurons and motoneurons, but only one of each is shown.

If the siphon is squirted repeatedly over the course of an hour, the animal soon habituates to the stimulus. It no longer retracts its gill. This short-term habituation results because the sensory neurons release progressively less transmitter upon the motoneurons.

(B) Long-term habituation

If the siphon is squirted repeatedly over days, the animal habituates faster and faster each day and eventually shows almost no response. This long-term habituation is due to a retraction of some of the synaptic terminals from the sensory neurons onto the motoneurons.

17.22 Synaptic Plasticity Underlying Habituation in Aplysia

Elements of the Aplysia gill withdrawal system are similarly capable of sensitization in which strong stimulation anywhere on the skin causes subsequent stimulations of the siphon to produce larger gill withdrawals (N. Dale et al., 1988). The strong stimulation of the skin activates a facilitating neuron that releases the transmitter serotonin onto the presynaptic nerve terminals in the gill withdrawal reflex circuit shown in Figure 17.22A. Serotonin boosts the activity in the circuit by prolonging the activity of the sensory neuron’s synapses onto the motoneuron, leading to a longer-lasting response (Y. Zhang et al., 2012).

The comparability of results obtained with diverse species of invertebrates indicates that, over a wide range of species, information can be stored in the nervous system by changes in both strength and number of synaptic contacts, confirming the hypotheses diagrammed in Figure 17.18. (For another example of memory research in invertebrates, see A Step Further: In Drosophila, Each Stage in Memory Formation Depends on a Different Gene on the website.) Next we’ll consider a simple neural circuit in the mammalian brain in which neural activity alters the strength of synaptic connections.
17.23 Long-Term Potentiation Occurs in the Hippocampus

(A) If axons in the circuit are stimulated only once every second, the size of the response in the postsynaptic neurons is quite stable. However, after a brief tetanus (a burst of electrical stimulation triggering hundreds or thousands of action potentials over 1–2 seconds), the size of the excitatory postsynaptic potential (EPSP) responses increases markedly and remains high throughout the recording period. This greater responsiveness is called long-term potentiation (LTP). (B) The top diagram shows the location of the hippocampal formation in a whole rat brain and in a horizontal section. The bottom diagram of the right hippocampal formation shows various neural pathways found in the hippocampal formation, many of which display LTP. (See the text for an explanation of CA1, CA2, and CA3.)

Synaptic Plasticity Can Be Measured in Simple Hippocampal Circuits

Modern ideas about neuroplasticity have their origins in the theories of Donald Hebb (1949), who proposed that when a presynaptic neuron repeatedly activates a postsynaptic neuron, the synaptic connection between them will become stronger and more stable (the oft-repeated maxim “cells that fire together wire together” captures the basic idea). Ensembles of neurons, or cell assemblies, linked via synchronized activity of these Hebbian synapses (see also Figure 7.22), could then act together to store memory traces (Kelso and Brown, 1986).

In the 1970s, researchers probing the properties of hippocampal circuitry discovered an impressive form of neuroplasticity that appeared to confirm Hebb’s theories about synaptic remodeling (Bliss and Lømo, 1973; Schwartzkroin and Wester, 1975). In their experiments, electrodes were placed within the rat hippocampus, positioned so that the researchers could stimulate a group of presynaptic axons and immediately record the electrical response of a group of postsynaptic neurons. Normal, low-level activation of the presynaptic cells produced stable and predictable excitatory postsynaptic potentials (EPSPs; see Chapter 3), as expected. But when the researchers applied a brief high-frequency burst of electrical stimuli (called a tetanus) to the presynaptic hippocampal neurons, thus inducing high rates of action potentials, the response of the postsynaptic neurons changed. Now the postsynaptic cells responded to normal levels of presynaptic activity by producing much larger EPSPs; in other words, the synapses appeared to have become stronger or more effective. This stable and long-lasting enhancement of synaptic transmission, termed long-term potentiation (LTP), is illustrated in Figure 17.23A. Interestingly, a weakening of synaptic efficacy—termed long-term depression—can also encode information. This phenomenon is discussed in A Step Further: Long-Term Depression Is the Converse of Long-Term Potentiation on the website.

We now know that LTP can be generated in conscious and freely behaving animals, in anesthetized animals, and in tissue slices and that LTP is evident in a variety of invertebrate and vertebrate species. LTP also lasts for weeks or more (Bliss and Gardner-Medwin, 1973). So, at least superficially, LTP appears to have the hallmarks of a cellular mechanism of memory. This hint at a cellular origin has prompted an intensive research effort, centered mainly on the rat hippocampus, aimed at understanding the molecular and physiological mechanisms by which learning may induce LTP.

sensitization A form of nonassociative learning in which an organism becomes more responsive to most stimuli after being exposed to unusually strong or painful stimulation.
cell assembly A large group of cells that tend to be active at the same time because they have been activated simultaneously or in close succession in the past.
Hebbian synapse A synapse that is strengthened when it successfully drives the postsynaptic cell.
tetanus An intense volley of action potentials.
long-term potentiation (LTP) A stable and enduring increase in the effectiveness of synapses following repeated strong stimulation.
The hippocampal formation consists of two interlocking C-shaped structures—the hippocampus itself and the dentate gyrus—along with the adjacent cortex (also called the hippocampal gyrus). On structural grounds, neuroscientists distinguish three major divisions within the hippocampus, labeled CA1, CA2, and CA3. It was in the main input pathway to the hippocampal formation (the perforant pathway, originating in nearby entorhinal cortex and terminating at synapses in dentate gyrus) that LTP was originally demonstrated. But LTP is also intensively studied in other hippocampal pathways, which are illustrated in Figure 17.22B, and it may be a property of all excitatory synapses (Malenka and Bear, 2004).

In CA1, LTP occurs at synapses that use the excitatory neurotransmitter glutamate, and it is critically dependent on a glutamate receptor subtype called the NMDA receptor (after its selective ligand, N-methyl-D-aspartate). Treatment with drugs that selectively block NMDA receptors completely prevents new LTP in the CA1 region, but it does not affect LTP that has already been established. As you might expect, these postsynaptic NMDA receptors—working in conjunction with related glutamate receptors called AMPA receptors—have some unique characteristics, which we discuss next.

**NMDA receptors and AMPA receptors collaborate in LTP**

During normal, low-level activity, the release of glutamate at a CA1 synapse activates only the AMPA receptors. The NMDA receptors cannot respond to the glutamate, because magnesium ions (Mg$^{2+}$) block the NMDA receptor’s integral calcium ion (Ca$^{2+}$) channel (FIGURE 17.24A); thus, few Ca$^{2+}$ ions can enter the
neuron. The situation changes, however, if larger quantities of glutamate are released (in response to a barrage of action potentials), thus stimulating the AMPA receptors more strongly. Because AMPA receptors admit sodium ions (Na⁺) when activated, the increased activation of AMPA receptors depolarizes the postsynaptic membrane, and if a threshold value of about –35 millivolts or so is reached, the Mg²⁺ plug is driven from the central channels of the NMDA receptors (FIGURE 17.24B). The NMDA receptors are now able to respond to glutamate, admitting large amounts of Ca²⁺ into the postsynaptic neuron. Thus, NMDA receptors are fully active only when gated by a combination of voltage (depolarization via AMPA receptors) and the ligand (glutamate).

The large influx of Ca²⁺ at NMDA receptors activates intracellular enzymes, called protein kinases, that alter or activate a variety of other proteins. One of these protein kinases is CaMKII (calcium/calmodulin-dependent protein kinase II), which affects AMPA receptors in several important ways (FIGURE 17.24B and C) (Kessels and Malinow, 2009; Lisman et al., 2012). Activated CaMKII causes more AMPA receptors to be produced and inserted into the postsynaptic membrane, and existing nearby AMPA receptors are induced to move to the active synapse (T. Takahashi et al., 2003). The membrane-bound AMPA receptors are also modified to increase their conductance of Na⁺ and K⁺ ions (Sanderson et al., 2008). The net effect of these changes, therefore, is to enhance the sensitivity of the synapse to released glutamate.

A second major effect of the activated protein kinases involves a substance called CREB (cAMP responsive element–binding protein). CREB is a transcription factor (a protein that binds to the promoter region of genes and causes those genes to be transcribed). CREB activation results in the increased expression of several genes, including those encoding AMPA receptors. This leads to an increase in the number of AMPA receptors in the postsynaptic membrane, making the synapse more responsive.

**protein kinase** An enzyme that adds phosphate groups (PO₄) to protein molecules.

**cAMP responsive element–binding protein (CREB)** A protein that is activated by cyclic AMP (cAMP) so that it now binds the promoter region of several genes involved in neural plasticity.
to change their rate of expression) that is activated by protein kinases, including CaMKII and chemical cousins like MAPK (mitogen-activated protein kinase), PKC (protein kinase C), and TK (tyrosine kinase). So, as shown in Figure 17.25, a direct result of the activation of NMDA receptors is the activation of CREB and changes in the expression of genes encoding a wide range of proteins. Because the affected genes may encode anything from new receptors and kinases to the structural building blocks used for changing the shape of the cell, this action can have profound and long-lasting consequences for the neuron.

The long-term changes in neurons after LTP range from the formation of additional synapses, and enhancement of existing ones, to the construction of whole new dendritic branches and dendritic spines (Malenka and Bear, 2004). In mice, genetic deletion of CREB impairs LTM but not STM (Bourtchuladze et al., 1994; Kogan et al., 1997). The earlier stages of LTP, lasting an hour or so, appear not to require protein synthesis, but thereafter, inhibition of protein synthesis prevents longer-lasting LTP (U. Frey et al., 1993; Krug et al., 1984). Furthermore, neurons can make proteins that selectively block CREB’s actions (Genoux et al., 2002; Mioduszewska et al., 2003), possibly providing a means to erase or inhibit the formation of unwanted memories. Much remains to be discovered about the many controls on long-lasting components of LTP.

Not all of the changes in LTP are postsynaptic. When the postsynaptic cell is strongly stimulated and its NMDA receptors become active and admit Ca\(^{2+}\), an intracellular process causes the postsynaptic cell to release a retrograde messenger—often a diffusible gas—that travels back across the synapse and alters the functioning of the presynaptic neuron (see Figure 17.24B). By affecting the presynaptic cell, the retrograde messenger ensures that more glutamate will be released into the synapse than previously, thereby strengthening the synapse. So, LTP involves active participation on both sides of the synapse. Nitric oxide (NO), carbon monoxide (CO), arachidonic acid, and nerve growth factor are among more than a dozen possible retrograde signals in LTP (J. R. Sanes and Lichtman, 1999).

In other locations in the hippocampus, such as the mossy fiber pathway (see Figure 17.23B), LTP can occur without NMDA receptor activity (E. W. Harris and Cotman, 1986), and some forms of LTP are blocked by drugs with completely different modes of action, such as opiate antagonists (Aroniadou et al., 1993; Derrick and Martinez, 1994). The diversity of mechanisms involved in LTP has complicated one of the central questions in LTP research, which we address next.
Is LTP a mechanism of memory formation?

Even the simplest learning involves circuits of multiple neurons and many synapses, and more-complex declarative and procedural memory traces must involve vast networks of neurons, so we are unlikely to conclude that LTP is the only mechanism of learning. However, LTP may be an important part of a multifaceted system for storing information. Evidence from several research perspectives—as we defined way back in Figure 1.2—implies LTP in memory:

1. Correlational observations  The time course of LTP bears strong similarity to the time course of memory formation (Lynch et al., 1991; Staubli, 1995). Covarying with memory, LTP can be induced within seconds, may last for days or weeks, and shows a labile consolidation period that lasts for several minutes after induction.

2. Somatic intervention experiments  In general, pharmacological treatments that interfere with basic physiological processes that contribute to LTP tend to impair learning. So, for example, NMDA receptor blockade interferes with performance in the Morris water maze (a test of spatial memory) and other types of memory tests (R. G. Morris et al., 1989). Drugs that inhibit CaMKII and other protein kinases also generally interfere with aspects of memory formation (M. R. Rosenzweig et al., 1992, 1993; Serrano et al., 1994). Because these same basic physiological processes are at work in many regions of the brain, in earlier research it was difficult to know exactly where and how the drugs were acting to affect memory. But more recently, regional genetic manipulations have enabled researchers to zero in on specific brain regions. Mice with one copy of the CaMKII gene knocked out can still form STMs, but they cannot form LTMs (Frankland et al., 2001). And knockout mice that lack functional NMDA receptors only in CA1 appear normal in many respects, but their hippocampi are incapable of LTP and their memory is impaired (Rampon et al., 2000). In a clever reversal, researchers have also shown that mice engineered to overexpress NMDA receptors in the hippocampus have enhanced LTP, and better-than-normal long-term memory (Y. P. Tang et al., 1999, 2001). (For the full story of these mice, known as Doogies, see A Step Further: How to Build a Doogie on the website.)

3. Behavioral intervention experiments  In principle, the most convincing evidence for a link between LTP and learning would be “behavioral LTP”: a demonstration that training an animal in a memory task can induce LTP in the brain. Such research is difficult because of uncertainty about exactly where to put the recording electrodes in order to detect any induced LTP. Nevertheless, several examples of successful behavioral LTP have been reported. Fear conditioning—for example, the repeated pairing of an aversive stimulus and a tone, eventually resulting in exaggerated reactions to the tone alone (see Figure 15.15)—produces clear LTP specifically in fear circuits in the amygdala and not elsewhere (McKernan and Shinnick-Gallagher, 1997; Rogan et al., 1997). And in the CA1 region of the hippocampus, a different form of aversive learning in rats has been shown to produce exactly the same electrophysiological changes, as well as changes in AMPA receptor accumulation, that are seen with conventionally induced LTP (Whitlock et al., 2006).

Taken together, the research findings support the idea that LTP is a kind of synaptic plasticity that underlies (or is very similar to) certain forms of learning and memory.

Some Simple Learning in Mammals Relies on Circuits in the Cerebellum

Although LTP may be a synaptic mechanism of memory, a more complete understanding of memory processes requires analysis of networks of neurons. Describing the complete circuit for even a simple learned behavior is very difficult in mammals because, in contrast to Aplysia, mammals have brains containing billions of neurons that are not organized in fixed circuits. So researchers focused on a very simple mammalian behavior: classical conditioning.
CHAPTER 17

associative learning  A type of learning in which an association is formed between two stimuli or between a stimulus and a response; includes both classical and instrumental conditioning.

instrumental conditioning or operant conditioning  A form of associative learning in which the likelihood that an act (instrumental response) will be performed depends on the consequences (reinforcing stimuli) that follow it.

classical conditioning  Also called Pavlovian conditioning. A type of associative learning in which an originally neutral stimulus (the conditioned stimulus, or CS)—through pairing with another stimulus (the unconditioned stimulus, or US) that elicits a particular response—acquires the power to elicit that response when presented alone. A response elicited by the US is called an unconditioned response (UR); a response elicited by the CS alone is called a conditioned response (CR).

Learning that involves relations between events—for example, between two or more stimuli, between a stimulus and a response, or between a response and its consequence—is called associative learning. This is in contrast to nonassociative learning, like habituation, that we described earlier in Aplysia. In one form of associative learning, instrumental conditioning (also called operant conditioning), an association is formed between the animal’s behavior and the consequence(s) of that behavior. An example of an apparatus designed to study instrumental learning is an operant conditioning apparatus (FIGURE 17.26A), often called a Skinner box after its originator, B. F. Skinner. Here, the conditioned instrumental response is pressing a bar to gain the reward of a food pellet.

In another form of associative learning, classical conditioning (also called Pavlovian conditioning), an initially neutral stimulus comes to predict an event. At the end of the nineteenth century, Ivan Pavlov (1849–1936) (FIGURE 17.26B) found that a dog would salivate when presented with an auditory or visual stimulus if the stimulus came to predict an event that normally caused salivation. If the experimenter rang a bell just before putting meat powder in the dog’s mouth, repeating this sequence a few times would cause the dog to respond to the bell itself by salivating. In this case the meat powder in the mouth is the unconditioned stimulus (US), which already evokes an unconditioned response (UR). The sound is the conditioned stimulus (CS), and the learned response to the CS alone (salivation in response to the bell in this example) is called the conditioned response (CR).

With this technique, rabbits can be conditioned to blink an eye in response to a tone. When a puff of air is applied to the cornea of a rabbit, the animal reflexively blinks. If the air puff (US) immediately follows an acoustic tone (CS), a simple conditioned response develops rapidly: the rabbit comes to blink (CR) when the tone is sounded. The basic circuit of the eye-blink reflex is simple, involving cranial nerves and some interneurons that connect their nuclei (FIGURE 17.27A). Sensory fibers from the cornea run along cranial nerve V (the trigeminal nerve) to its nucleus in the brainstem. From there, some interneurons send axons to synapse on other cranial nerve motor nuclei (VI and VII), which in turn activate the muscles of the eyelids, causing them to close.

Early studies showed that destruction of the hippocampus has little effect on the acquisition or retention of the conditioned eye-blink response in rabbits (Lockhart and Moore, 1975). Therefore, the hippocampus is not required for this conditioning. Interestingly, eye-blink training that involves a delay between the CS and US does rely on the hippocampus; see A Step Further: The Hippocampus Is Needed for...
Complex Eye-Blink Conditioning (on the website.) Instead, as we mentioned earlier in the chapter, researchers found that learning-related increases in the activity of individual neurons are specific to the cerebellum and associated structures. A large research effort eventually described a cerebellar circuit that is both necessary and sufficient for eye-blink conditioning.

The trigeminal (V) pathway that carries information about the corneal stimulation (the US) to the cranial motor nuclei also sends axons to the brainstem (specifically a structure called the inferior olive). These brainstem neurons, in turn, send axons called climbing fibers to synapse on cerebellar neurons in a region called the interpositus nucleus. The same cells also receive information about the auditory CS by a pathway through the auditory nuclei and other brainstem nuclei (Figure 17.27B). So the US and CS converge in the interpositus nucleus of the cerebellum. After conditioning, the occurrence of the CS—the tone—has an enhanced effect on the cerebellar neurons, so they now trigger eye blink even in the absence of an air puff (Figure 17.27C).

Local cooling or drugs that block the neurotransmitter GABA (gamma-aminobutyric acid, the transmitter used at synapses in the cerebellar circuit) have the effect of reversibly shutting down the interpositus nucleus. If this manipulation is performed at the beginning of training, then no conditioning occurs until after the effect wears off. Conversely, if animals are fully trained before treatment, subsequent injection of a GABA antagonist causes the conditioned behavior to disappear, along with its electrophysiological signature, until after the drug effect wears off. On the basis of these and other experiments, the complete eye-blink conditioning circuit is now un-
derstood, and the cerebellum’s interpositus nucleus appears to be the key location for storing this type of memory (R. F. Thompson and Steinmetz, 2009).

As we discussed earlier, studies on human subjects are consistent with the animal research on eye-blink conditioning. Furthermore, by rapidly stimulating sensory cranial nerves in the circuit during training in human volunteers, researchers have been able to show that LTP probably plays a role in human eye-blink conditioning (Mao and Evinger, 2001). Unsurprisingly, other cases of conditioning also depend on cerebellar mechanisms. For example, conditioned leg flexion (in which the animal learns to withdraw a leg on hearing a tone) is cerebellum-dependent (Donegan et al., 1983; Voneida, 1990). Studies of humans with cerebellar damage indicate that the cerebellum is important for conditioning across several domains, including conditioning of emotions like fear, and aspects of cognitive learning (Timman et al., 2009).

In the Adult Brain, Newly Born Neurons May Aid Learning
There is now no doubt that new neurons are produced in the brains of adult mammals, including humans, as we discussed in Chapter 7 (C. G. Gross, 2000). This adult neurogenesis occurs primarily in the dentate gyrus of the hippocampal formation (FIGURE 17.28), and new dentate neurons that survive and grow ultimately receive inputs from entorhinal cortex via the perforant pathway (see blue pathway in Figure 17.23B), extending their own axons and forming glutamatergic synapses (Toni et al., 2008). Anatomically, therefore, the new neurons appear to integrate into the functional circuitry of the hippocampus and adjacent cortex (Bruel-Jungerman et al., 2007), which we’ve seen play a role in forming new memories.

In experimental animals, neurogenesis and the survival of young neurons can be enhanced by a variety of factors, such as exercise, experience in an enriched environment, or training in a memory task (E. Gould, Beylin et al., 1999; Kempermann et al., 1997; Ming and Song, 2005; Prickaerts et al., 2004; Waddell and Shors, 2008). Reproductive hormones and experiences also potently influence neurogenesis (Ga-Lea, 2008; Pawluski and Galea, 2007). What’s more, newly generated neurons in the dentate gyrus are more plastic, showing enhanced LTP, compared with older neurons (Marín-Burgin et al., 2012). Although these observations are tantalizing, clear demonstrations that the new cells have significant functions in behavior—especially learning and memory—have been somewhat elusive.

Rats given a drug that is lethal to newly born neurons are reportedly impaired on tests of conditioning, but only when there is an interval between the CS and
the US (Shors et al., 2001). As we discussed earlier, this form of conditioning is believed to rely on hippocampal function, so the finding that it is impaired when neurogenesis is prevented suggests that the role of neurogenesis in memory may be limited to hippocampus-dependent forms of memory. Neurogenesis has also been implicated in other forms of hippocampus-dependent learning, such as spatial memory and fear conditioning in some (but not all) studies (Kee et al., 2007; Saxe et al., 2006; Winocur et al., 2006). In a study using mice with a conditional knockout—a gene that can be selectively deactivated in adulthood in specific tissues—researchers found that turning off neurogenesis in the brains of adults resulted in a marked impairment in spatial learning with little effect on other behaviors (C. L. Zhang et al., 2008).

The impaired learning that accompanies reduced adult neurogenesis, however it is caused, is consistent with a role for new neurons in learning. But it is always possible that the manipulations have a general effect, making the animals feel ill, for example, that might affect their performance. However, one lab used genetic manipulations to increase the survival of newly generated neurons in the dentate, resulting in improved performance (Sahay et al., 2011). These animals showed enhanced hippocampal LTP, which was expected since younger neurons display greater synaptic plasticity (Marin-Burgin et al., 2012). These mice were also better at one particular task: discriminating between two similar environments (Sahay et al., 2011). Adult neurogenesis is also seen in the olfactory bulb (see Chapter 9), and activation of newly generated neurons enhances olfactory learning and memory (Alonso et al., 2012). Thus it seems clear that neurons born in adulthood play a role in learning and memory.

Learning and Memory Change as We Age

Understanding the impact of aging on cognition is a pressing issue; by 2030, there will be more than twice as many senior citizens alive as there were in 2000. In people and other mammals, normal aging brings a gradual decline in some but not all aspects of learning and memory (N. D. Anderson and Craik, 2000; Gallagher and Rapp, 1997; Lister and Barnes, 2009). For some tasks, differences in motivation, earlier education, and other confounding factors may masquerade as age-related memory problems. So experiments on memory in the elderly must be carefully constructed to control for alternate explanations.

What kinds of tasks reliably show decrements in performance with aging? Normal elderly people tend to show some memory impairment in tasks of conscious recollection that require effort (Hasher and Zacks, 1979) and that rely primarily on internal generation of the memory rather than on external cues (Craik, 1985). Giving elderly subjects easily organized task structures, or cues, can often raise their performance to the level of the young. Although working memory, and the ability to form new episodic and declarative memories typically declines with age, existing memories such as autobiographical memory and semantic knowledge, tend to remain stable (Hedden and Gabrieli, 2004). If vocabulary is tested in isolation, older adults outperform younger adults (D. C. Park et al., 2002), but on tests of executive function, even individuals in their 40s are likely to show age-related decline (Rhodes, 2004).

As we age, we also experience some decreases in spatial memory and navigational skills (Barnes and Penner, 2007; E. S. Rosenzweig and Barnes, 2003). Similarly, aged rats show decrements in the eight-arm radial maze (see Figure 17.16A) compared with younger animals (Mizumori et al., 1996; M. A. Rossi et al., 2005). Along with other memory impairments, spatial-memory problems may become much more severe in dementias like Alzheimer’s disease, which is discussed in detail in Chapter 7. In these severe cases of amnesia, memory performance may resemble that of an infant: shown a familiar object in a new location, patients continue to search for it in the old location, even passing over the object in plain sight in the new site. They appear to remember the search procedure and not the object being sought (M. Moscovitch, 1985).

conditional knockout  A gene that can be selectively deactivated, either in specific tissues and/or at a specific stage of development.
Age-related impairments of memory have several causes

Why do some measures of learning and memory decline with age, while others remain intact? There are a number of ways in which neural changes may affect learning and memory during aging (Craik and Salthouse, 2007; Lister and Barnes, 2009). Some of the major contributors to memory problems in old age include

- **Impairments of encoding and retrieval**  Older subjects show less cortical activation than younger subjects when encoding or retrieval is self-initiated. In **FIGURE 17.29**, less frontal and temporal activity is seen in the older subjects while learning new faces (Grady et al., 1995), but when recognizing faces (a retrieval task that is not self-initiated, because retrieval is prompted by viewing stimuli), the elders’ brain activity is comparable to that of the younger subjects. Some studies find increased activation in elderly subjects, possibly due to recruitment of neurons to compensate for difficulty or just more-diffuse or nondifferentiated activity (Grady and Craik, 2000).

- **Loss of neurons and/or neural connections**  The brain gradually loses weight after the age of 30, and some parts of the brain, such as frontal cortex (Raz, 2000), lose a larger proportion of volume or weight than other parts. Although not all investigators agree, age-related memory impairment may involve steady loss of synapses and neurons in the hippocampus and cortex (Geinisman et al., 1995; J. H. Morrison and Hof, 2007; Simic et al., 1997).

- **Problems with cholinergic neurotransmission**  Two subcortical regions—known as the septal complex and the nucleus basalis of Meynert (NBM)—provide profuse cholinergic inputs to the hippocampus and cortex. Memory impairment in Alzheimer’s disease seems to be caused by the loss of these cholinergic afferents to the cortex (McGeer et al., 1984; Rossor et al., 1982). Drug treatments that enhance acetylcholine transmission improve aspects of memory performance in human subjects (Furey et al., 2000; Ricciardi et al., 2009). Acetylcholine levels are reduced in old rats that show memory impairment in the water maze, compared with either old rats that perform well or young rats (Gallagher et al., 1995).

Can the effects of aging on memory be prevented or alleviated?

The search for anti-aging interventions and **nootropics**—drugs that enhance cognitive function—is an area of intense activity. Pharmacological approaches include the use of drugs, such as donepezil (Aricept), that inhibit cholinesterase, the enzyme that breaks down acetylcholine. The resultant increase in cholinergic transmission in the forebrain has a positive effect on memory and cognition in mild to moderate cases of Alzheimer’s (Ringman and Cummings, 2006). Compounds in a different class, called

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**nootropics** A class of drugs that enhance cognitive function.
ampakines, act via glutamate receptors to improve hippocampal LTP (Rex et al., 2006);ampakines are under study as potential memory-enhancing therapeutics. And research suggests that one particular protein kinase—PKMζ (the squiggle is the Greek letter zeta)—is needed for long-term maintenance of both hippocampal LTP and cortical memory traces (Shema et al., 2007, 2009), raising the possibility that compounds that alter this kinase could be highly selective memory drugs. The list of other possible targets for developing memory-boosting drugs grows longer every day.

Rats raised in enriched conditions show improved handling of stress and associated reduction in glucocorticoid secretion, and lower chronic levels of glucocorticoids may protect hippocampal function during aging (Sapolsky, 1993). Enriched experience also increases the release of nerve growth factor (NGF) in the hippocampus (Mohammed et al., 1993; Ottoson et al., 1995). So lifelong environmental enrichment may have strongly protective effects on cognitive functions, such as memory, later in life. Longitudinal research tracking thousands of people suggests several general lifestyle factors that can help reduce the risk of cognitive decline in old age (Schaie, 1994), including:

- **Living in favorable environmental circumstances** Getting an above-average education, pursuing occupations that involve high complexity and low routine, earning above-average income, and maintaining intact families
- **Involvement in complex and intellectually stimulating activities** Extensive reading, travel, attendance at cultural events, continuing-education activities, and participation in clubs and professional associations
- **Having a spouse/partner with high cognitive status**

Because so much of the brain is involved in the creation, storage, and retrieval of memories, a full understanding of learning and memory will require an enormous research effort at many levels of analysis, from molecular processes to cognitive studies of special cases like Henry Molaison. At age 82, more than 50 years after his life-shattering surgery, Henry died. In a final act of generosity to a field of science that he helped launch, Henry donated his brain for further study. Through webcasting technology, the slicing of Henry’s brain into sections was viewed live by thousands of people (see thebrainobservatory.ucsd.edu/hm), and a series of more than 2000 sections will eventually be made available. To the end, although he could remember so little of his entire adult life, Henry was courteous and concerned about other people (FIGURE 17.30). He remembered the surgeon he had met several times before his operation: “He did medical research on people….What he learned about me helped others too, and I'm glad about that” (Corkin, 2002, p. 158). Henry never knew how famous he was, or how much his dreadful condition taught us about learning and memory; yet despite being deprived of one of the most important characteristics of a human being, he held fast to his humanity.

**The Cutting Edge**

**Artificial Activation of an Engram**

We’ve seen that experience can alter the strength of synapses and, for simple behaviors like habituation in a simple organism like *Aplysia*, we know exactly which synapse weakens as habituation proceeds. But in more-complicated animals like mammals, the physical basis of a memory formed by learning a particular task—the engram—probably involves changes in many neurons and in many synapses. In other words, the memory is more likely encoded by changes in the activity of a circuit of neurons, not just one neuron (much less one synapse). If so, then reactivating the neurons encoding the memory might be experienced as remembering. Several groups have tested this idea in mice, where genetic tools permit remarkable control over neuronal activity. In one such demonstration, researchers were able to mark precisely the neurons that were activated when mice were subjected to fear conditioning (X. Liu et al., 2012). Mice were exposed to a particular context A, placed in a box with a white plastic floor in a dimly lit room with black walls and a faint smell of almonds. The mice explored the chamber and showed no signs of being afraid (FIGURE 17.31A and B). Next the mice were taught to be afraid of a very different context B (a box with a wire grid floor in a brightly lit room with white walls and the smell of vinegar) by being exposed to an auditory tone followed by a mildly painful electrical shock to the feet. As expected, the mice quickly learned to freeze in response to the auditory tone (see Figure 15.15). Most important, these mice had been genetically modified so that whenever neurons in the dentate gyrus (DG) of the hippocampus were active, they would start producing channelrhodopsin, a protein that would excite those cells, and only those cells, when exposed to blue light (see Figure (Continued))
3.22). If the activity of this subset of DG neurons was responsible for the mice finding context B frightening, then reactivating those neurons should cause the mice to freeze in fear, even when they were in a completely different context.

To test this idea, the mice were put in context A, where they had never been shocked. As before, they showed no signs of being afraid. But, when fiber optics illuminated their DG with blue light, the mice froze, as if afraid. It was as though the mice were experiencing the other context, B, when the DG neurons that had been active in B were reactivated by the blue light. Turning the light off again caused the animals to resume activity, indicating that they remained unafraid of context A (FIGURE 17.31C). It wasn’t just that light-induced activation of any random set of DG neurons induced fear, because when blue light reactivated DG neurons that had been active in a third (nonfearful) context, C, the animals did not freeze (FIGURE 17.31D). Rather, it appeared that the activity of that subset of DG neurons caused the mice to experience context B, which they had learned to fear. Experimenters had activated an artificial memory.

17.31 Artificial Activation of an Engram
(After X. Liu et al., 2012.)

Transgenic mice were constructed so that any neurons that were active started producing channelrhodopsin. These neurons would now be excited when exposed to blue light, provided by fiber optics directed at the dentate gyrus (DG) of the hippocampus.

First the mice were fed a special diet that blocked production of channelrhodopsin while they explored context A. They did not act afraid.

The mice were then taken off the special diet so that those DG neurons that are active during fear conditioning would produce channelrhodopsin.

After being returned to the diet that prevents any new production of channelrhodopsin, the mice were returned to context A to see if reactivation of the DG neurons that had been active during fear conditioning would induce freezing.

After they had learned to fear context B, reexposure to context A still did not induce freezing unless the hippocampus was stimulated with blue light (“On”), reactivating DG neurons that had been active in context B.

Blue light stimulation of a set of DG neurons that had been active in a third, non-fearful context, C, did not induce freezing. Fear is not induced by reactivation of any arbitrary set of DG neurons, just those that had been active during fear conditioning.
**Recommended Reading**


**Go to 7e.biopsychology.com for study questions, quizzes, flashcards, and other resources**

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**17 Visual Summary**

1. **The hippocampus, mammillary bodies, and dorsal thalamus** are part of a network that must be intact to form new **declarative memories**—memories that we can declare to others. Damage to these regions can cause **amnesia**, the impairment of memory. Review Figure 17.1

2. **Removal of the hippocampus and nearby cortex left patient H.M.** unable to form declarative memories that lasted more than a few minutes. He could, however, learn new **skills** such as mirror tracing, showing his **nondeclarative** (or **procedural**) memory for perceptual and motor behaviors was intact. Review Figures 17.2–17.4

3. **Declarative memory** consists of **semantic memory** of facts and **episodic memory** (or **autobiographical memory**) of particular incidents in the past. Brain damage can remove one type of declarative memory without affecting the other, indicating the two kinds of memories are stored separately. Review Figures 17.5, 17.13, and 17.17, Activity 17.1

4. **Nondeclarative memory**, which includes **skill learning, priming, and conditioning**, is demonstrated through performance. Most tests of memory in nonhuman animals are for nondeclarative memory, an exception being the **non-matching-to-sample task** in monkeys. Review Figures 17.5, 17.11, and 17.12

5. Memories are classified by how long they last. **Iconic memory** is a very brief recollection of sensations. **Short-term memory** (STM), sometimes called **working memory**, lasts only a few minutes. Then the memory is either lost or transferred to **long-term memory** (LTM), which may last a lifetime. The successive processes transferring information from one place to the other are **encoding, consolidation, and retrieval**. Memories are subject to distortion during recall and **reconsolidation**. Review Figures 17.6–17.9

6. Different kinds of learning depend on different brain regions. **Spatial learning** requires an intact hippocampus, while motor skills rely on the **basal ganglia**, and object recognition relies on the visual cortex. Review Figures 17.15–17.17, Activity 17.2

(Continued)
Nonassociative learning includes habituation, while associative learning includes classical conditioning (Pavlovian conditioning) and instrumental conditioning (operant conditioning). In the sea slug *Aplysia*, habituation is due to a weakening of the synapse between the sensory neuron and the motoneuron. Review Figures 17.21 and 17.22.

Strong emotion can affect the strength of memories, as in posttraumatic stress disorder (PTSD). Review Box 17.1.

Long-term potentiation (LTP) is a lasting increase in amplitude of the response of neurons caused by brief high-frequency stimulation of their afferents (tetanus). In the hippocampus, LTP depends on the activation of NMDA receptors, which induces an increase in the number of postsynaptic AMPA receptors and greater neurotransmitter release. These are examples of Hebbian synapses, which become stronger if they successfully drive the postsynaptic cell, and weaker if they are unsuccessful. Review Figures 17.23–17.25, Activity 17.3, Animation 17.2, Video 17.3.

Conditioning of the eye-blink response in the rabbit is crucially dependent on the cerebellum. This simple mammalian system provides a model for understanding the formation of associations in the mammalian brain. Review Figure 17.27.