Learning as the Storage of Memories

Some one-celled animals "learn" surprisingly well, for example, to avoid swimming toward a light where they have received an electric shock before. I have placed the term *learn* in quotation marks because such simple organisms lack a nervous system; their behavior changes briefly, but if you take a lunch break during your subject's training, when you return, you will have to start all over again. Such a temporary form of learning may help an organism avoid an unsafe area long enough for the danger to pass or linger in a place where food is more abundant. But without the ability to make a permanent record, you could not learn a skill, and experience would not help shape who you are. We will introduce the topic of learning by examining the problem of storage.

Amnesia: The Failure of Storage and Retrieval

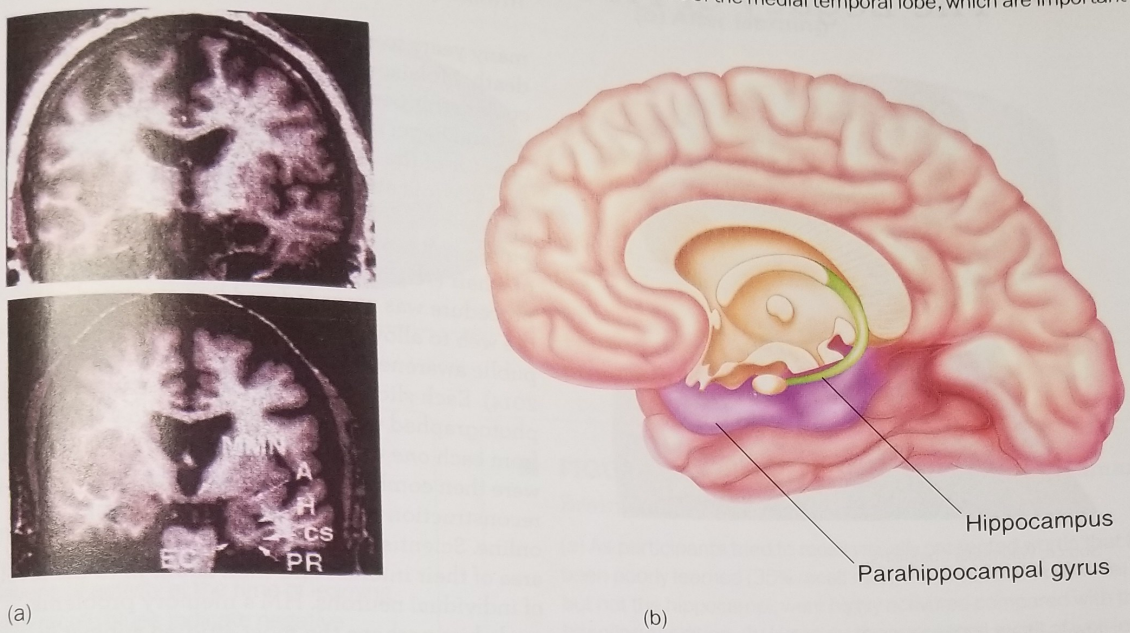
HM's symptoms are referred to as *anterograde amnesia,* an impairment in forming new memories. (*Anterograde* means "moving forward.") This was not HM's only memory deficit; the surgery also caused *retrograde amnesia,* the inability to remember events prior to impairment. His retrograde amnesia extended from the time of surgery back to about the age of 16; he had a few memories from that period, but he did not remember the end of World War II or his own graduation, and when he returned for his 35th high school reunion, he recognized none of his classmates. Better memory for earlier events than for recent ones may seem implausible, but it is typical of patients who have brain damage like HM's. How far back the retrograde amnesia extends depends on how much damage there is and which specific structures are damaged.

HM's surgery damaged or destroyed the hippocampus, nearby structures that along with the hippocampus make up the *hippocampal formation,* and the amygdala. Figure 12.1 shows the location of these structures. Because they are on or near the inside surface of the temporal lobe, they form part of what is known as the medial temporal lobe (remember that *medial* means "toward the middle"). Because HM's surgery was so extensive, it is impossible to tell which structures are responsible for the memory functions that were lost. Studies of patients with varying degrees of temporal lobe damage have helped determine which structures are involved in amnesia and, therefore, in memory. Henry died in 2008 at the age of 82, but he continues to contribute, as the accompanying Application explains.

The hippocampus consists of several substructures with different functions. The part known as *CA1* provides the primary output from the hippocampus to other brain areas; damage in that part of both hippocampi results in moderate anterograde amnesia and only minimal retrograde amnesia. If the damage includes

FIGURE 12.1 Temporal Lobe Structures Involved in Amnesia.

(a) HM's brain (top left) and a normal brain (below). You can see that the amygdala (A), hippocampus (H), and other structures labeled in the normal brain are partly or completely missing in HM's brain. (b) Structures of the medial temporal lobe, which are important in learning. (The frontal lobe is to the left.)



(a) (b)

Sources: (a) From "HM's Medial Temporal Lobe Lesion: Findings From Magnetic Resonance Imaging," by S. Corkin, D. G. Amaral, R. G. González, K. A. Johnson, and B. T. Hyman, 1997, *Journal of Neurosicence, 17*, pp. 3964–3979. Copyright © 1997 by the Society for Neuroscience. Used with permission. (b) Adapted with permission from "Remembrance of Things Past," by D. L. Schacter and A. D. Wagner, *Science, 285*, pp. 1503–1504. Illustration: K. Sutliff. © 1999 American Association for the Advancement of Science. Reprinted with permission from AAAS.

the rest of the hippocampus, anterograde amnesia is severe. Damage to the entire hippocampal formation results in retrograde amnesia extending back 15 years or more (J. J. Reed & Squire, 1998; Rempel-Clower, Zola, Squire, & Amaral, 1996; Zola-Morgan, Squire, & Amaral, 1986). More extensive retrograde impairment occurs with broader damage or deterioration, like that seen in Alzheimer's disease, Huntington's disease, and Parkinson's disease, apparently because memory storage areas in the cortex are compromised (Squire & Alvarez, 1995).

Mechanisms of Consolidation and Retrieval

HM's memory impairment consisted of two problems: consolidation of new memories and, to a lesser extent, retrieval of older memories. *Consolidation* is the process in which the brain forms a more or less permanent physical representation of a memory. *Retrieval* is the process of accessing stored memories—in other words, the act of remembering. When a rat presses a lever to receive a food pellet or a child is bitten by a dog or you skim through the headings in this chapter, the experience is held in memory at least for a brief time. But just like the phone number that is forgotten when you get a busy signal the first time you dial, an experience does not necessarily become a permanent memory; and if it does, the transition takes time. Until the memory is consolidated, it is particularly fragile. New memories may be disrupted just by engaging in another activity, and even older memories are vulnerable to intense experiences such as emotional trauma or electroconvulsive shock treatment (a means of inducing convulsions, usually in treating depression). Researchers divide memory into two stages, *short-term memory* and *long-term memory*. Long-term memory, at least for some kinds of learning, can be divided into two stages that have different durations and occur in different locations (Figure 12.2), as we will see later (McGaugh, 2000).

> "Most memories, like humans and wines, do not mature instantly. Instead they are gradually stabilized in a process referred to as consolidation."
>
> —Yadin Dudai

An animal study clearly demonstrates that the hippocampus participates in consolidation. Rats were trained in a water maze, a tank of murky water from which they could escape quickly by learning the location of a

APPLICATION

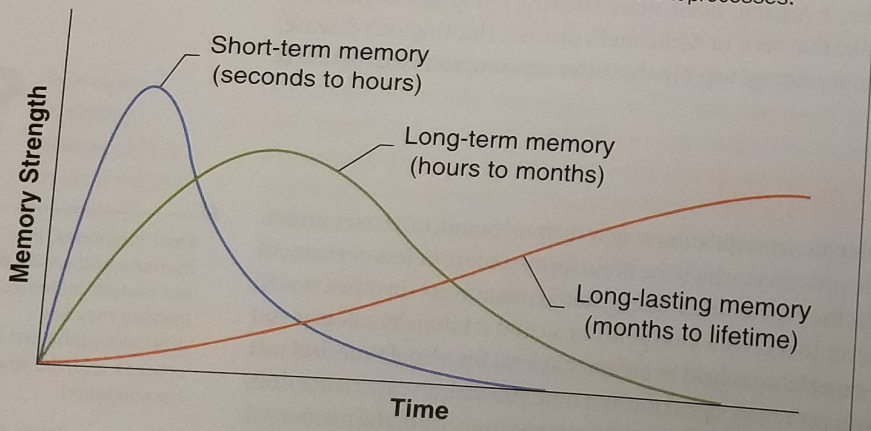
The Legacy of HM

Source: Wikimedia Commons.

Not only did Henry Molaison devote much of his life to numerous scientific investigations, but his brain will continue to be the subject of study for many years to come (Lafee, 2009). Soon after his death, Molaison's preserved brain was in a plastic cooler strapped in a seat on a flight from Boston to San Diego; in the next seat was Jacopo Annese, director of the Brain Observatory at the University of California at San Diego. After several months of preparation, Annese and his colleagues dissected Molaison's brain into slices as thin as the width of a hair (70 μm). The 53-hour, uninterrupted procedure was recorded and live-streamed over the web to allow scientific scrutiny and to increase public awareness and engagement (Annese et al., 2014). Each slice of HM's brain was microscopically photographed with such resolution that the data from each *one* would fill 200 DVDs. The data were then combined into a three-dimensional reconstruction of the brain, which is available online. Scientists can navigate through it to the area of their interest and then zoom in to the level of individual neurons. HM's memory problems made him perhaps the most studied subject in neuroscience. Ironically, the man who could not remember will never be forgotten.

FIGURE 12.2 Stages of Consolidation.

Making a memory permanent involves multiple stages and different processes.



Source: Reprinted with permission from "Memory—A Century of Consolidation," by J. L. McGaugh, *Science, 287*, pp. 248–251. Copyright 2000 American Association for the Advancement of Science.

platform submerged just under the water's surface (Figure 12.3; Riedel et al., 1999). Then, for seven days the rats' hippocampi were temporarily disabled by a drug that blocks receptors for the neurotransmitter glutamate. Eleven days later—plenty of time for the drug to clear the rats' systems—they performed poorly compared with control subjects (Riedel et al.). Researchers have been able to "watch" the consolidation happening in humans, using brain scans and event-related potentials. Presenting words or pictures activated the hippocampus and adjacent cortex; how well the material was remembered later could be predicted from how much activation occurred in those areas during stimulus presentation (Figure 12.4; Alkire, Haier, Fallon, & Cahill, 1998; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Fernández et al., 1999).

Animals that were given the glutamate-blocking drug at the time of testing instead of immediately after training also had impaired recall in the water maze, indicating that the hippocampus has a role in retrieval as well as consolidation. Researchers have used PET scans to confirm that the hippocampus also retrieves memories in humans (D. L. Schacter, Alpert, Savage, Rauch, & Albert, 1996; Squire et al., 1992). Figure 12.5 shows increased activity in the hippocampi while the research participants recalled words learned during an experiment. The involvement of the hippocampus in

FIGURE 12.3 A Water Maze.

The rat learns to escape the murky water by finding the platform hidden just below the surface.

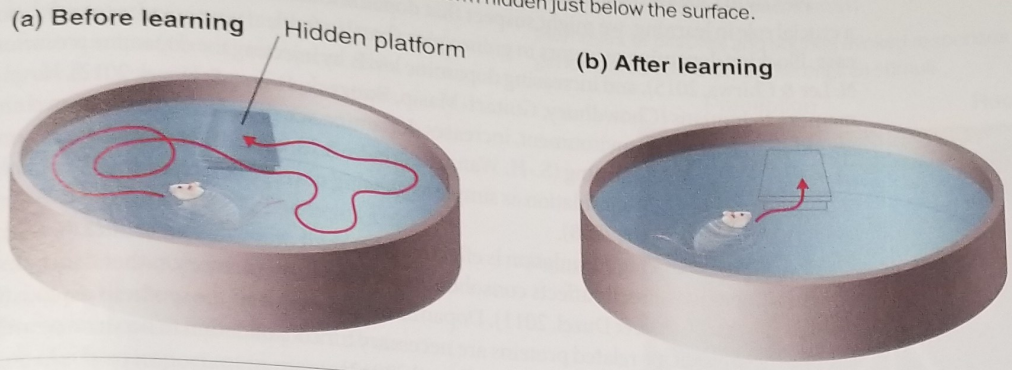
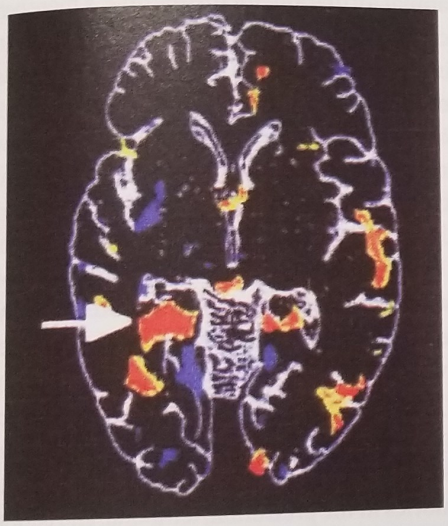


FIGURE 12.4 Hippocampal Activity Related to Consolidation.

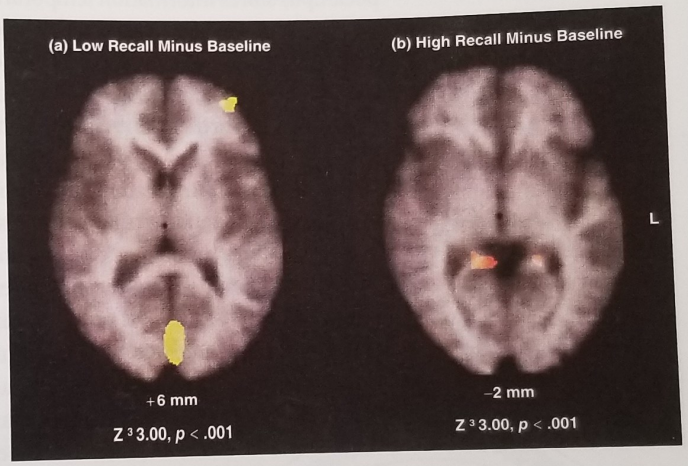
The arrow is pointing to the hippocampal region. Reds and yellows indicate positive correlations of activity at the time of learning with later recall; blues indicate negative correlations.



Source: From "PET Imaging of Conscious and Unconscious Memory," by M. T. Alkire, R. J. Haier, J. H. Fallon, and S. J. Barker, 1996, *Journal of Consciousness Studies, 3*, pp. 448–462.

FIGURE 12.5 Hippocampal Activity in the Human Brain During Retrieval.

(a) As participants tried to recall visually presented words that had been poorly learned (35% recall rate), the prefrontal and visual areas, but not the hippocampi, were highly activated compared with the baseline condition. (b) However, the successful recall of well-learned words (79% recall rate) activated both hippocampal areas.



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retrieval seems inconsistent with HM's ability to recall earlier memories. But the memories that patients with hippocampal damage can recall are of events that occurred at least two years before their brain damage. Many researchers have concluded that the hippocampal mechanism plays a time-limited role in consolidation and retrieval, a point we will examine shortly. This diminishing role of the hippocampus would explain why older memories suffer less than recent memories after hippocampal damage.

The prefrontal area is also active during learning and retrieval, and some researchers think that it directs the search strategy required for retrieval (Buckner & Koutstaal, 1998). Indeed, the prefrontal area is active during effortful attempts at retrieval, whereas the hippocampus is activated during successful retrieval (see

Figure 12.5; D. L. Schacter et al., 1996). We will look at the role of the frontal area again when we consider working memory and Korsakoff syndrome.

We saw in Chapter 5 that rewards such as drugs increase activity in dopamine neurons. Because reward plays a crucial role in learning, we might suspect that dopamine has some function in learning, and that is indeed the case. Blocking dopamine receptors in guinea pigs shortly after learning impairs consolidation and memory (K.-N. Lee & Chirwa, 2015), and increasing dopamine levels by injecting the dopamine precursor levodopa improves memory in humans (Chowdhury, Guitart-Masip, Bunzeck, Dolan, & Düzel, 2012). Novel experience, such as exploring an unfamiliar environment, increases dopamine activity; placing rats in a novel environment before or after learning improves learning (S.-H. Wang, Redondo, & Morris, 2010). In humans, learning can be increased by dopamine-enhancing stimulation as simple as viewing novel photographs from *National Geographic* (Fenker, Frey, Schuetze, & Heipertz, 2008).

Dopamine-enhancing stimulation is effective whether it occurs before or after the learning experience; this is because dopamine directly affects consolidation of long-term memory, rather than by improving short-term memory (Lisman, Grace, & Duzel, 2011). Dopamine release initiates the synthesis of proteins in the postsynaptic neuron. These plasticity-related proteins are necessary for consolidation to occur, as we will see later, and drugs that block their synthesis inhibit learning (Clopath, 2012).

Dopamine does not signal rewards so much as it signals *errors in prediction*. Firing increases in dopamine neurons only if the reward is unexpected—either of greater value than usual or occurring when it has been infrequent (Schultz, 2016). If the reward is expected, the firing rate remains the same and it declines if the reward is less than expected. In other words, evolution has tailored learning specifically to help us cope with changes in our environment and in our circumstances.

Where Memories Are Stored

? Is there a place where memories are stored?

The hippocampal area is not the permanent storage site for memories. If it were, patients like HM would not remember anything that happened before their damage occurred. According to most researchers, the hippocampus stores information temporarily in the hippocampal formation; then, over time, a more permanent memory is consolidated elsewhere in the brain. A study of mice that had learned a spatial discrimination task supported the hypothesis: Over 25 days of retention testing, metabolic activity progressively decreased in the hippocampus and increased in the cortical areas (Bontempi, Laurent-Demir, Destrade, & Jaffard, 1999).

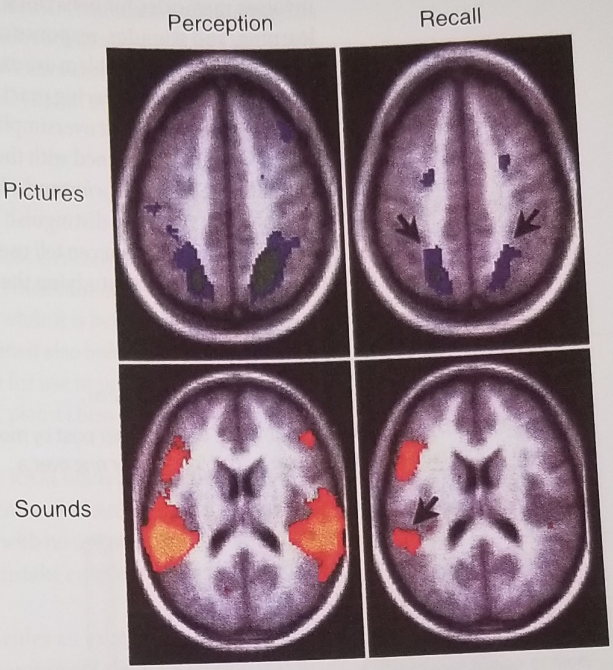
To explore further the relationship between these two areas, Remondes and Schuman (2004) severed the pathway that connects CA1 of the hippocampus with the cortex. The lesions did not impair the rats' performance in a water maze during training or 24 hours (hr) later, but after 4 weeks the rats had lost their memory for the task. The results supported the hypothesis that short-term memory depends on the hippocampus but long-term memory requires the cortex and an interaction over time between the two. To pin down the window of vulnerability of the memory, the researchers lesioned two additional groups of animals at different times *following* training. Those lesioned 24 hr after training were impaired in recall four weeks later, but those whose surgery was delayed until three weeks after training performed as well as the controls. This progression apparently takes longer in humans. Christine Smith and Larry Squire (2009) used fMRI to image the brain's activity while subjects recalled news events from the past 30 years. Activity was greatest in the hippocampus and related areas as subjects recalled recent events, declined as they recalled events as far back as 12 years, and stabilized after that. At the same time, activity increased progressively with older memories in the prefrontal, temporal, and parietal cortex. So, your brain works rather like your computer when it transfers volatile memory from RAM to the hard drive—it just takes a lot longer.

In Chapter 3, you learned that when Wilder Penfield (1955) stimulated association areas in the temporal lobes of surgery patients, he often evoked visual and auditory experiences that seemed like memories. We speculated that memories might be stored there, and more recent research has supported that idea, with memories for sounds activating auditory areas and memories for pictures evoking activity in the occipital region (Figure 12.6; M. E. Wheeler, Petersen, & Buckner, 2000). You also saw in Chapter 9 that when we learn a new language, it is stored near Broca's area. Naming colors (which requires memory) activates temporal lobe areas near where we perceive color; identifying pictures of tools activates the hand motor area and an area in the left temporal lobe that is also activated by motion and by action words (A. Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995; A. Martin et al., 1996); and spatial memories appear to be stored in the parietal area and verbal memories in the left frontal lobe (F. Rösler, Heil, & Henninghausen, 1995). Thus, all memories are not stored in a single area, nor is each memory distributed throughout the brain. Rather, different memories are in different cortical areas, apparently according to where the information they are based on was processed.

An interesting example is the cells involved in place memory. *Place cells*, which increase their rate of firing when the individual is in a specific location in the environment, are found in the hippocampus. Each cell has a place field (overlapping somewhat with others), and together these cells form a map of the environment. This map develops during the first few minutes of exploration; the cells' fields are then remapped on entering a new environment, but they are restored on returning to the original location (Figure 12.7; Guzowski, Knierim, & Moser, 2004; M. A. Wilson & McNaughton, 1993). The fields are dependent on spatial cues in the environment, including visual, tactile, and even olfactory cues (Shapiro, Tanila, & Eichenbaum, 1997). Place cells do more than indicate an individual's current location. For example, they contribute the context of location that is so important in memories of events (D. M. Smith & Mizumori, 2006). They also provide spatial memory required for planning navigation; as rats paused at choice points in a maze with which they were well experienced, cells with place fields in the alternative sections fired in sequence, as if the rats were simulating the two choices (Johnson & Redish, 2007). Functional MRI has confirmed that humans have place cells; their activity is so precise that the investigators could determine the subject's "location" in a computer-generated virtual environment (Hassabis et al., 2009).

FIGURE 12.6 Functional MRI Scans of Brains During Perception and Recall.

Memories of pictures and sounds evoked responses in the same general areas (arrows) as the original stimuli.



Source: From "Memory's Echo: Vivid Remembering Reactivates Sensory-Specific Cortex," by M. E. Wheeler et al., *Proceedings of the National Academy of Sciences, USA*, 97, pp. 11125–11129, fig. 1c, d, e, f, p. 11127. © 2000 National Academy of Sciences, USA.

Two Kinds of Learning

Learning researchers were in for a revelation when they discovered that HM could readily learn some kinds of tasks (Corkin, 1984). One was mirror drawing, in which the individual uses a pencil to trace a path around a pattern, relying solely on a view of the work surface in a mirror. HM improved in mirror-drawing ability over three days of training, and he learned to solve the Tower of Hanoi problem (Figure 12.8). But he could not remember learning either task, and on each day of practice he denied even having seen the Tower puzzle before (N. J. Cohen, Eichenbaum, Deacedo, & Corkin, 1985; Corkin, 1984). What this means, researchers realized, is that there are two categories of

? What are the two kinds of learning?

FIGURE 12.7 Recordings From Place Cells in a Rat in a Circular Runway.

The recordings are from seven different place cells, indicated by different colors. Note that each cell responds when the rat is in a particular part of the runway. (Due to cue similarities in a circular apparatus, cells occasionally respond on the opposite side of the circle.)

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memory processing. *Declarative memory* involves learning that results in memories of facts, people, and events that a person can verbalize or declare. For example, you can remember being in class today, where you sat, who was there, and what was discussed. Declarative memory includes a variety of subtypes, such as *episodic memory* (events), *semantic memory* (facts), *autobiographical memory* (information about oneself), and *spatial memory* (the location of the individual and of objects in space). *Nondeclarative memory* involves memories for behaviors; these memories result from procedural or skills learning, emotional learning, and stimulus-response conditioning. Learning mirror tracing or how to ride a bicycle or solve the Tower of Hanoi problem are examples of nondeclarative learning or, more specifically, procedural or skills learning; remembering practicing the tasks involves declarative learning. Another way of putting it, which is admittedly a bit oversimplified, is that declarative memory is informational, while nondeclarative memory is more concerned with the control of behavior. Just as we have *what* and *where* pathways in vision and audition, we have a *what* and a *how* in memory.

The main reason to distinguish between the two types of learning is that they have different origins in the brain; studying them can tell us something about how the brain carries out its tasks. For years, it looked like we were limited to studying the distinction in the rare human who had brain damage in just the right place; hippocampal lesions did not seem to affect learning in rats, so researchers thought that rats did not have an equivalent of declarative memory. But it just took selecting the right tasks. R. J. McDonald and White (1993) used an apparatus called the radial arm maze, a central platform with several arms radiating from it (Figure 12.9). Rats with damage to both hippocampi could learn the simple conditioning task of going into any lighted arm for food. But if every arm was baited with food, the rats could not remember which arms they had visited and repeatedly returned to arms where the food had already been eaten.

FIGURE 12.8 The Tower of Hanoi Problem.

The task is to relocate the rings in order onto another post by moving them one at a time and without ever placing a larger ring over a smaller one.

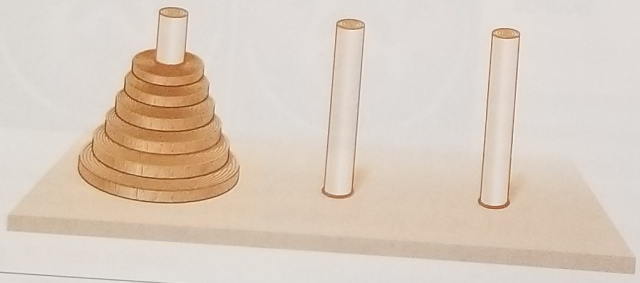
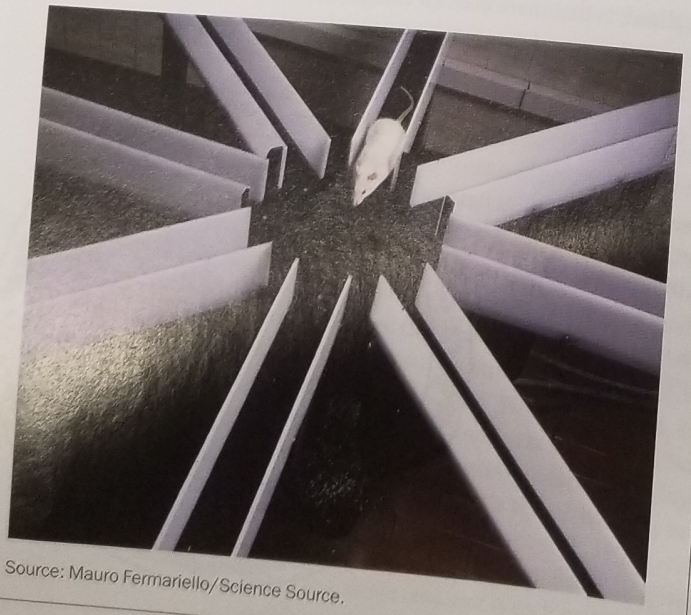


FIGURE 12.9 A Radial Arm Maze.

The rat learns where to find food in the maze's arms. The arms are often enclosed by walls.



Source: Mauro Fermariello/Science Source.

Conversely, rats with damage to the *striatum* could remember which arms they had visited but could not learn to enter lighted arms. Because Parkinson's disease and Huntington's disease damage the basal ganglia (which include the striatum), people with these disorders have trouble learning procedural tasks, such as mirror tracing or the Tower of Hanoi problem (Gabrieli, 1998). Incidentally, the term *declarative* seems inappropriate with rats; researchers have often preferred the term *relational memory*, which implies that the individual must learn relationships among cues, an idea that applies equally well to humans and animals.

You already know that the amygdala is important in emotional behavior, but it also has a significant role in nondeclarative emotional learning. Bechara and his colleagues (1995) studied a patient with damage to both amygdalae and another with damage to both hippocampi. The researchers attempted to condition an emotional response in the patients by sounding a loud boat horn when a blue slide was presented but not when the slide was another color. The patient with amygdala damage reacted emotionally to the loud noise, indicated by increased skin conductance responses (see Chapter 8). He could also tell the researchers which slide was followed by the loud noise, but the blue slide never evoked a skin conductance increase; in other words, conditioning was absent. The patient with hippocampal damage showed an emotional response and conditioning, but he could not tell the researchers which

paired with. This neural distinction between declarative learning and nondeclarative emotional learning may well explain how an emotional experience can have a long-lasting effect on a person's behavior even though the person does not remember the experience.

The amygdala has an additional function that cuts across learning types. Both positive and negative emotions enhance the memorability of any event; the amygdala strengthens even declarative memories about emotional events, apparently by increasing activity in the hippocampus. Electrical stimulation of the amygdala activates the hippocampus, and it enhances learning of a non-emotional task, such as a choice maze (McGaugh, Cahill, & Roozendaal, 1996). In humans, memory for both pleasant and aversive emotional material is related to the amount of activity in both amygdalae while viewing the material (Cahill et al., 1996; Hamann, Ely, Grafton, & Kilts, 1999).

Working Memory

The brain stores a tremendous amount of information, but information that is merely stored is useless. It must be available, not just when it is being recalled into awareness but when the brain needs it for carrying out a task. *Working memory* provides a temporary "register" for information while it is being used. Working memory holds a password you just looked up long enough for you to type it in; it also holds information retrieved from long-term memory while it is integrated with other information for use in problem solving and decision making. Without working memory, we could not do long division, plan a chess move, or even carry on a conversation.

Think of working memory as like the RAM in your computer. The RAM holds information temporarily while it is being processed or used, but the information is stored elsewhere on the hard drive. But we should not take any analogy too far. Working memory has a very limited capacity (with no upgrades available), and information in working memory fades within seconds. So, if you make a mistake entering the password you just looked up, you'll probably have to look it up again.

The *delayed match-to-sample task* described in Chapter 11 provides an excellent means of studying working memory. During the delay period, cells remain active in one or more of the association areas in the temporal and parietal lobes, depending on the nature of the stimulus (Constantinidis & Steinmetz, 1996; Fuster & Jervey, 1981; Miyashita & Chang, 1988). Cells in these areas apparently help maintain the memory of the stimulus, but they are not the location of working memory. If a distracting stimulus is introduced during the delay period, the altered firing in these locations ceases abruptly, but the animals are still able to make the correct choice (Constantinidis & Steinmetz, 1996; E. K. Miller, Erickson, & Desimone, 1996). Cells in the prefrontal cortex have several attributes that make them better candidates as working memory specialists. Not only do they increase firing during a delay, but they also maintain the increase despite a distracting stimulus (E. K. Miller et al., 1996). Some respond selectively to the correct stimulus (di Pellegrino & Wise, 1993; E. K. Miller et al.). Others respond to the correct stimulus, but only if it is presented in a specific position in the visual field; they apparently integrate information from cells that respond only to the stimulus with information from cells that respond to the location (Rao, Rainer, & Miller, 1997). Prefrontal damage impairs humans' ability to remember a stimulus during a delay (D'Esposito & Postle, 1999). All these findings suggest that the prefrontal area plays the major role in working memory.

Although the prefrontal cortex serves as a temporary memory register, its function is apparently more than that of a neural blackboard. In Chapters 3 and 8, you learned that damage to the frontal lobes impairs a person's ability to govern his or her behavior in several ways. Many researchers believe that the primary role of the prefrontal cortex in learning is as a central executive. That is, it manages certain kinds of behavioral strategies and decision making and coordinates activity in the brain areas involved in the perception and response functions of a task, all the while directing the neural traffic in working memory (Wickelgren, 1997).

CONCEPT CHECK

Take a Minute to Check Your Knowledge and Understanding

- What determines the symptoms and the severity of symptoms of amnesia?
- Describe the two kinds of learning and the related brain structures.
- Working memory contributes to learning and to other functions. How?

Brain Changes in Learning

How do neurons change during learning?

Learning is a form of neural plasticity that changes behavior by remodeling neural connections. Specialized neural mechanisms have evolved to make the most of this capability. We will look at them in the context of long-term potentiation.

Long-Term Potentiation

More than 50 years ago, Donald Hebb (1940) stated what has become known as the *Hebb rule:* If an axon of a presynaptic neuron is active while the postsynaptic neuron is firing, the synapse between them will be strengthened. We saw this principle in action during the development of the nervous system, when synaptic strengthening helped determine which neurons would survive; some of that plasticity is retained in the mature individual. Researchers have long believed that to understand learning as a physiological process, they would have to figure out what happens at the level of the neuron and, particularly, at the synapse.

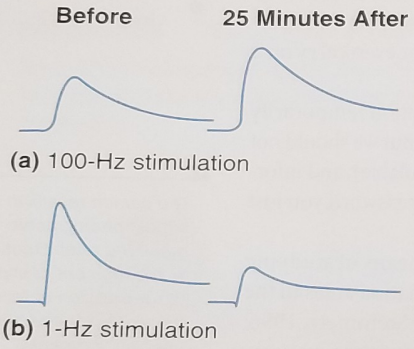
Long-term potentiation (LTP) is a persistent strengthening of synapses that results from the simultaneous activation of presynaptic neurons and postsynaptic neurons (Cooke & Bliss, 2006). LTP can be induced in the laboratory by stimulating both neurons at the same time, or by stimulating the presynaptic neuron adequately to cause the postsynaptic neuron to fire. As you can see in Figure 12.10a, the postsynaptic neuron's response to a test stimulus is much stronger following induction of LTP. What is remarkable about LTP is that it can last for hours in tissue cultures and months in laboratory animals (Cooke & Bliss). LTP has been studied mostly in the hippocampus, but it also occurs in several other areas, including the visual, auditory, and motor cortex. So LTP appears to be a characteristic of much of neural tissue, at least in the areas most likely to be involved in learning.

Neural functioning requires weakening synapses as well as strengthening them. *Long-term depression (LTD)* is a decrease in the strength of synapses that occurs when stimulation of presynaptic neurons is insufficient to activate the postsynaptic neurons (Cooke & Bliss, 2006). Potentiation can be depressed in a postsynaptic neuron by applying a low-frequency pulse to the presynaptic neuron for a few minutes, causing the presynaptic neuron to fire but not the postsynaptic neuron (Figure 12.10b). LTD is believed to be the mechanism the brain uses to modify memories and to clear old memories to make room for new information (Stickgold, Hobson, Fosse, & Fosse, 2001).

Activity in presynaptic neurons also influences the sensitivity of nearby synapses. If a weak synapse and a strong synapse on the same postsynaptic neuron are active simultaneously, the weak synapse will be potentiated; this effect is called *associative long-term potentiation* (Figure 12.11). Associative LTP is usually studied in isolated brain tissue with artificially created weak and strong synapses, but it has important behavioral implications, which is why it interests us. Electric shock evokes a strong response in the lateral amygdala, where fear is registered, while an auditory stimulus produces only a minimal response there. Rogan, Stäubli, and LeDoux (1997) repeatedly paired a tone with shock to the feet of rats. Because of this procedure, the tone alone began to evoke a significantly increased response in the amygdala, as well as an emotional "freezing" response in the rats. You may recognize this scenario as an example of *classical conditioning;* we could easily change the labels in Figure 12.11 from "Strong synapse" to "Electric shock" and from "Weak synapse" to "Auditory tone." Researchers believe that associative LTP is the basis of classical conditioning, and Rogan et al.'s results support that view. LTP, LTD, and associative LTP can all be summed up in the expression "Cells that fire together wire together."

■ **FIGURE 12.10** LTP and LTD in the Human Brain.

The graphs show excitatory postsynaptic potentials in response to a test stimulus before and after repeated stimulation. (a) 100-hertz (Hz) stimulation produced LTP. (b) 1-Hz stimulation produced LTD, which blocked the potentiation established earlier.



Source: From "Long-Term Modifications of Synaptic Efficacy in the Human Inferior and Middle Temporal Cortex," by W. R. Chen et al., *Proceedings of the National Academy of Sciences, USA, 93,* pp. 8011–8015. Copyright 1996 National Academy of Sciences, USA. Used with permission.

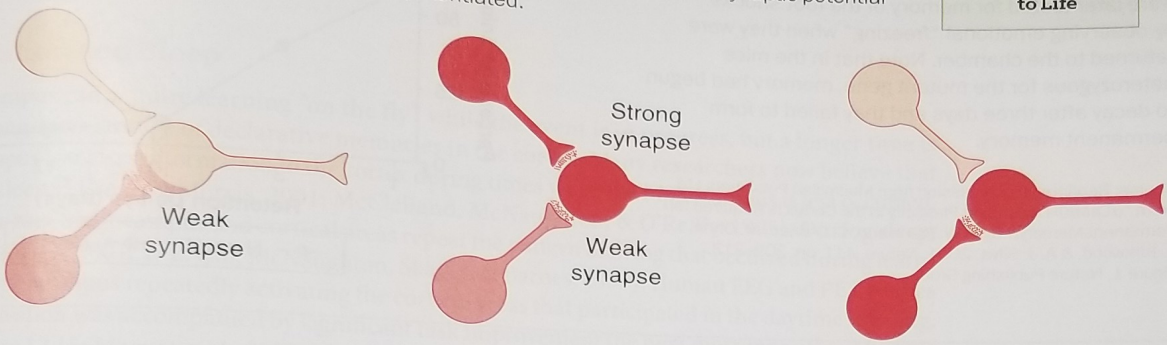
How LTP Happens

LTP has been studied most often in the neurons connecting CA1 and CA3 of the hippocampus, and we will use those findings as our model here without going into the variations that occur in other areas of the brain. LTP is induced through a cascade of events at the synapse. In CA1 (and in most locations) the neurotransmitter involved is glutamate, which is detected by two types of receptors: the AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor and the NMDA (N-methyl-d-aspartic acid) receptor. Initially, glutamate activates AMPA receptors but not NMDA receptors, because they are blocked by magnesium ions

FIGURE 12.11 Associative LTP.

(a) Initially, the weak synapse produces only a very small excitatory postsynaptic potential. (b) Simultaneous activation of a strong synapse along with activity in the weak synapse induces associative LTP. (c) Following associate LTP, the much larger excitatory postsynaptic potential indicates that the weak synapse has been potentiated.

Figures Brought to Life



(a) Stimulation by weak synapse (test)

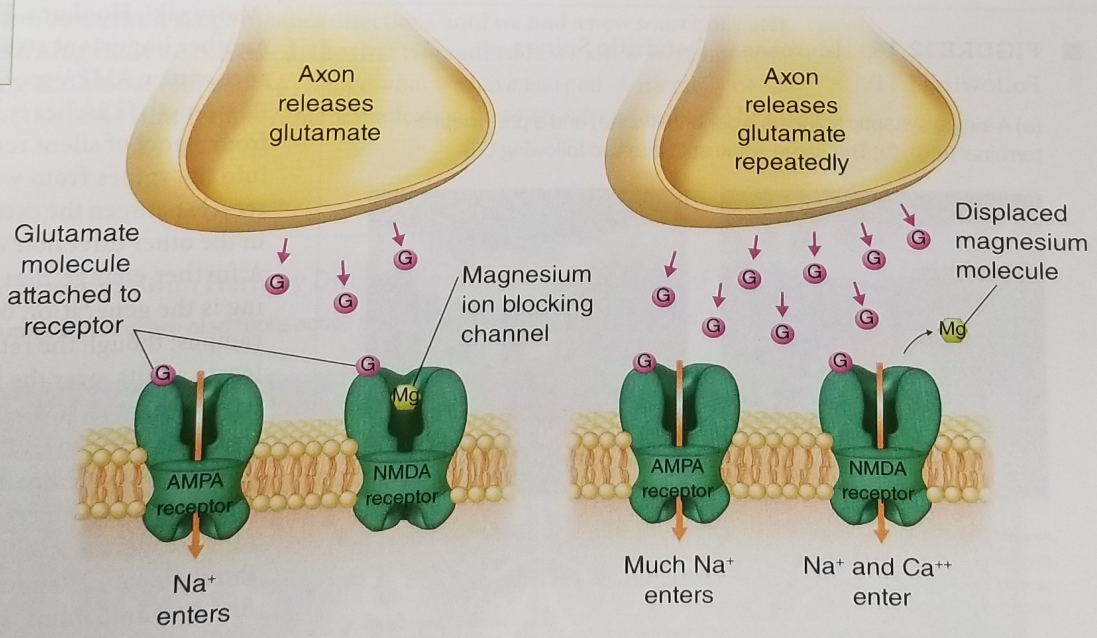
(b) Stimulation by weak and strong synapse (induction)

(c) Stimulation by strengthened synapse (test)

FIGURE 12.12 Participation of Glutamate Receptors in LTP.

(a) Initially, glutamate activates the AMPA receptors but not the NMDA receptors, which are blocked by magnesium ions. (b) However, if the activation is strong enough to partially depolarize the postsynaptic membrane, the magnesium ions are ejected. The NMDA receptor can then be activated, allowing sodium and calcium ions to enter.

Figures Brought to Life



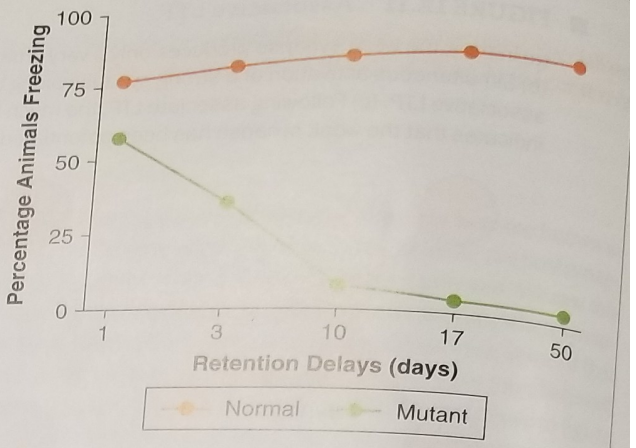
(a) Dendrite

(b) Dendrite, much depolarized

(Figure 12.12). During LTP induction, activation of the AMPA receptors by the first few pulses of stimulation partially depolarizes the membrane, and this dislodges the magnesium ions. The resulting large influx of calcium ions activates a host of *protein kinases,* enzymes that alter or activate other proteins (Lüscher & Malenka, 2012). One of the protein kinases, CaMKII (calcium/calmodulin-dependent kinase II) is required for LTP.

FIGURE 12.13 Retention in Normal and αCaMKII- Deficient Mice Over Time.

Mice given foot shocks in a conditioning chamber were later tested for memory of the foot shocks by observing emotional "freezing" when they were returned to the chamber. Note that in the mice heterozygous for the mutant gene, memory had begun to decay after three days and they failed to form permanent memory.



Source: Reprinted by permission from Macmillan Publishers Ltd. From "αCaMKII-Dependent Plasticity in the Cortex Is Required for Permanent Memory," by P. W. Frankland, C. O'Brien, M. Ohno, A. Kirkwood, & A. J. Silva, 2001, *Nature, 411*, pp. 309–313. Figure 1. Nature Publishing Group.

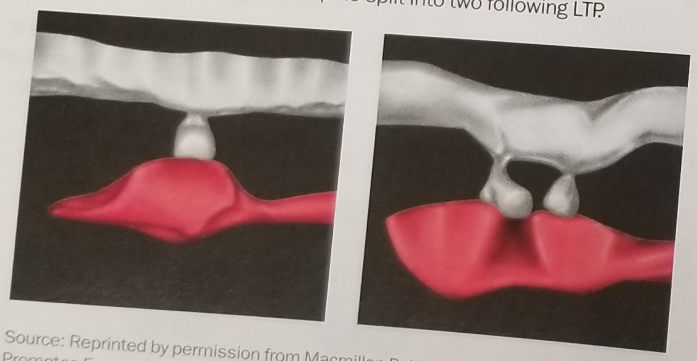
Mice with two mutant, nonfunctioning genes for the alpha form of CaMKII fail to show LTP; those with one mutant and one functioning gene do show LTP, but it is not consolidated into long-term memory (Figure 12.13; Frankland, O'Brien, Ohno, Kirkwood, & Silva, 2001). Several plasticity-related genes are activated as well (Kelleher, Govindarajan, & Tonagawa, 2004); they along with newly activated proteins begin producing structural changes in the synapse (Lüscher & Malenka).

? How does the brain grow during learning?

Within 45–60 minutes after LTP, postsynaptic neurons develop dramatically increased numbers of *dendritic spines*, outgrowths from the dendrites that partially bridge the synaptic cleft and make the synapse more sensitive (Figure 12.14; N. Toni, Buchs, Nikonenko, Bron, & Muller, 1999). Existing spines also enlarge or split down the middle to form two spines (Matsuzaki, Honkura, Ellis-Davies, & Kasai, 2004). Another important structural change is the appearance of new AMPA receptors, which increase synaptic strength (Lüscher & Malenka, 2012). These come from a pool of silent receptors that are transported into the spines from within the dendrite; they can recycle between the cytoplasm and the membrane or in the other direction within mere tens of minutes. A further change that occurs in support of learning is the generation of new neurons in the hippocampus; though the rate of neurogenesis is relatively low in adults, over the life span new neurons add up to an estimated 10%–20% of the population (Jacobs, van Praag, & Gage, 2000). Numerous studies show that learning is impaired by blocking neurogenesis and enhanced by increasing new cell birth. New neurons are more active than mature ones, have a lower threshold for LTP induction, and are better at making fine discriminations, such as distinguishing between the contexts in which reward occurs and does not occur (Yau, Li, & So, 2015). It also appears that the new neurons contribute to the shift in memory from the hippocampus to cortex and interfere with the LTP established in the hippocampus to clear the way for new memories (Kitamura & Inokuchi, 2014). Blocking neurogenesis with X-radiation prolongs hippocampal LTP and delays completion of the transfer to the cortex by as many as 28 days.

FIGURE 12.14 Increase in Dendritic Spines Following LTP.

(a) A single synaptic spine on a dendrite (white) and a presynaptic terminal (red). (b) The same spine split into two following LTP.



Source: Reprinted by permission from Macmillan Publishers Ltd. Based on "LTP Promotes Formation of Multiple Spine Synapses Between a Single Axon Terminal and a Dendrite," by N. Toni et al., *Nature, 402* (6706), pp. 421–425. Nature Publishing Group.

? How do the roles of the hippocampus and the cortex differ?

With all that growth, you might suspect that there would be some increase in the volume of the brain areas that are involved in LTP. In fact, this does happen to some extent. London taxi drivers, who are noted for

their ability to navigate the city's complex streets entirely from memory, spend about two years learning the routes before they can be licensed to operate a cab. Maguire and her colleagues (2000) used MRI to scan the brains of 16 drivers. The posterior part of their hippocampi, known to be involved in spatial navigation, was larger than in males of similar age. (Overall hippocampal volume did not change; their anterior hippocampi were smaller.) The difference was greater for cabbies who had been driving for the longest time, which we would expect if the difference was caused by experience.

Consolidation and Sleep

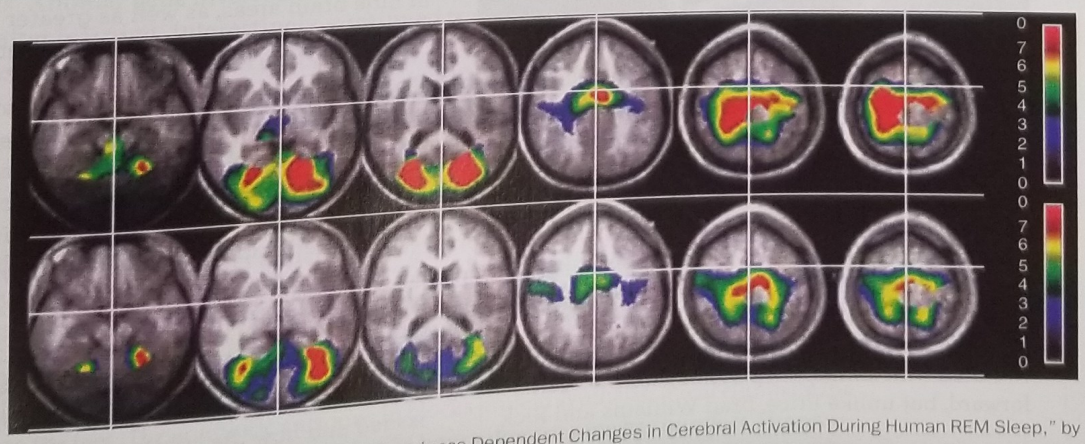
The hippocampus can acquire learning "on the fly" while the event is in progress, but a longer time is needed for long-term storage of declarative memories in the cortex. Many researchers now believe that the hippocampus transfers information to the cortex during times when the hippocampus is less occupied, even during sleep (Lisman & Morris, 2001; McClelland, McNaughton, & O'Reilly, 1995). During sleep, neurons in the rats' hippocampus and cortical areas repeat the pattern of firing that occurred during learning (Louie & Wilson, 2001; Y.-L. Qin, McNaughton, Skaggs, & Barnes, 1997). Human EEG and PET studies showed the hippocampus repeatedly activating the cortical areas that participated in the daytime learning, and this reactivation was accompanied by significant task improvement the next morning without further practice (Figure 12.15; Maquet et al., 2000; Wierzynski, Lubenov, Gu, & Siapas, 2009). Even a daytime nap of around 90 minutes is enough to evoke this kind of activity in the hippocampus and improve performance on a word-association test (Studte, Bridger, & Mecklinger, 2015). Presumably, "offline" replay provides the cortex the opportunity to undergo LTP at the more leisurely pace it requires (Lisman & Morris, 2001). During sleep, more than 100 genes increase their activity; many of those have been identified as major players in protein synthesis, synaptic modification, and memory consolidation (Cirelli, Gutierrez, & Tononi, 2004).

Changing Our Memories

As hard as the brain works to make memories "permanent," it is still important that these records not be inscribed in stone. Things change; the waterhole we learned was reliable over several visits is now becoming progressively more stagnant, so we must range in other directions until we find a new source of water. And sometimes erroneous learning must be corrected; the first two redheads we knew were hot tempered, and it will take meeting additional redheads to change what we have learned. A memory needs to be stable to be useful, but at the same time it must remain malleable; there are several ways the brain accomplishes this.

FIGURE 12.15 PET Scans of Brain Activity During Sleep Following Learning.

Areas previously active during learning are also more active during sleep in the trained subjects, but not in the untrained subjects.



Source: Reprinted by permission from Macmillan Publishers Ltd. From "Experience-Dependent Changes in Cerebral Activation During Human REM Sleep," by P. Maquet et al., 2000, *Nature Neuroscience, 3*, pp. 831–855, fig. 2, p. 833. Nature Publishing Group.

Extinction

The first is *extinction*. The experimenter sounds a tone just before delivering a puff of air to your eye; after just a few trials, you blink just because you hear the tone. This doesn't happen simply because you understand that the air blast is coming; it occurs more quickly than you can make a voluntary response. Then the experimenter sounds the tone several times without administering the puff of air. Slowly the tone loses its power to make you blink. The memory is not gone; if the experimenter repeats the puff of air, you will be back to blinking every time you hear the tone. Nor is this an example of forgetting. Rather, extinction involves new learning; one indication is that, like LTP, extinction requires activation of NMDA receptors, and blocking these receptors eliminates extinction (Santini, Muller, & Quirk, 2001).

Forgetting

Most memories dissipate at least somewhat over time if they are not used frequently. We invariably regard memory loss from *forgetting* as a defect, but researchers are finding clues that the brain actively removes useless information to prevent the saturation of synapses with information that is not called up regularly or has not made connections with other stored memories. One way the brain cleans house apparently involves the enzyme protein phosphatase 1 (PP1), a product of the *PP1* gene. To study PP1's effect, researchers created transgenic mice (see Chapter 4) with genes for a particularly active form of PP1 inhibitor (Genoux et al., 2002). The genes were inducible, which means that the researchers could activate them at any time. Mice were trained in a water maze, and then the genes were turned on in the transgenic animals; 6 weeks later, the control subjects' memory for the task was completely absent, while the transgenic mice had forgotten very little. You may remember from your introductory psychology course that for most tasks, spreading out practice sessions (*distributed practice*) leads to better learning

APPLICATION

Total Recall

urce: iStock/michellegibson

ost of us would like to remember more and rget less. But a few years ago, Jill Price wrote neuropsychologist James McGaugh at the iversity of California, Irvine, asking for help cause she couldn't forget; she can remember at she did and what was happening in the world practically every day of her life, and she is often mented by bad memories (J. Marshall, 2008; E. S. rker, Cahill, & McGaugh, 2006). Two years later o men with similar memory capabilities came ward, but unlike Price, Brad Williams and Rick Baron can keep their memories at bay (Elias, 2008; D. S. Martin, 2008). Williams uses his memory in his work as a radio news reporter; Baron is unemployed but supports himself in part by winning contests that utilize his memory for facts. The researchers are eager to understand what fuels this unusual ability, because the knowledge could help the memory impaired. Of the 33 super-memory people confirmed by McGaugh's lab, 11 have undergone MRI scans; these revealed structural differences in nine brain areas, as well as greater white matter connections between areas (LePort et al., 2012).

The interesting thing is that these individuals do no better than other people on memorization tests; they just don't suppress their memories once they're formed. So what might be going on in these individuals? One indication is that inadequate inhibition might be involved because they show signs of compulsive behavior. Each is a devoted collector—years of TV guides, rare record albums, hundreds of TV show tapes—and Baron arranges all the bills in his wallet according to the city of the Federal Reserve Bank where they were issued and how the sports teams in that city did.

IN THE NEWS

ENHANCING SOLDIERS' LEARNING WITH NEUROSTIMULATION

In 2016, the U.S. military began a new project aimed at applying knowledge of how learning occurs in the brain in order to improve performance in a variety of tactical areas (DARPA Public Affairs, 2017). The Targeted Neuroplasticity Training (TNT) program is funding research at several academic institutions to develop invasive and noninvasive methods for coaxing the brain to form connections in areas involved in cognitive functioning. Arizona State University scientist Stephen Helms Tillery will be using a technology called transdermal electrical neuromodulation, a noninvasive method of electrically activating parts of the nervous system by stimulating nerves through the skin (B. Wang, 2017). Helms Tillery's work will focus on stimulating the trigeminal nerve to activate a brain nucleus called the locus coeruleus, which releases the neurotransmitter norepinephrine. Scientists know that norepinephrine is activated as part of the "fight or flight" response and people show enhanced sensory functioning as part of their response to stress. Participants in Helms Tillery's studies will receive neuromodulation while performing a variety of perceptual and decision-making tasks, with the goal of increasing activity in related brain areas and improving performance on these tasks. Eventually, the military plans to use trigeminal nerve stimulation to enhance training of marksmen and drone pilots. Researchers at other institutions will be stimulating the vagus nerve, either through transdermal electrical neuromodulation or using invasive methods, to promote language learning; the technique could be useful, for example, in training intelligence experts (DARPA Public Affairs, 2017). Because military applications of neuroenhancements are controversial, the TNT program has funded a workshop on the ethical implications of this and related investigations.

THOUGHT QUESTIONS

1. How might neuromodulation impact the performance of military personnel in combat or noncombat roles?
2. How can electrical stimulation through the skin be used to activate portions of the brain?
3. What is one ethical issue that you think should be considered in these types of neuroscience applications?

For the news story, visit edge.sagepub.com/garrett5e and select the Chapter 12 study resources.

than *massed practice*. When the inhibitor genes were turned on during training, this advantage disappeared, which suggests that the reason distributed practice is superior is that PP1's effects accumulate over massed practice trials. Another gene involved in forgetting is *Drac1(V12)*. Its protein product, Rac, causes memory to decay after learning. Interestingly, continued training suppresses Rac, which means that additional practice has a dual benefit (Shuai et al., 2010).

Efficient memory involves a balance between remembering and forgetting. Later in this chapter we will see how devastating memory impairment can be. The accompanying Application shows that there is another side to the coin as well.

Reconsolidation

Consolidation is a progressive affair extending over a relatively long period of time. During that time, the memory is vulnerable to disruption from several sources, including electroconvulsive shock and drugs that interfere with protein synthesis. In recent years, researchers have come to realize that each time a memory is retrieved, it must be *reconsolidated*, and during that time the memory becomes even more vulnerable (Dudai, 2004). For example, Nader, Schafe, and LeDoux (2000) conditioned a fear response (freezing) to a tone in mice by pairing the tone with electric shock to the feet. The antibiotic anisomycin blocks protein synthesis; it will eliminate the fear memory if it is injected shortly after learning, but injection 24 hours after training has no effect. However, as many as two weeks later, anisomycin eliminated the fear learning if the researchers induced retrieval of the memory by presenting the tone again (without the shock). You might very well wonder why the brain would

give up protection of a consolidated memory during retrieval. Apparently, reopening a memory provides the opportunity to refine it, correct errors, and modify your emotional response to people who rubbed you the wrong way the first time you met them (J. L. C. Lee, 2009; McKenzie & Eichenbaum, 2011). Reconsolidation may even have therapeutic usefulness. It can be used to eliminate a learned fear response in humans, and (as you will see in Chapter 14) could provide an effective tool for erasing fear memories in people with posttraumatic stress disorder (D. Schiller et al., 2010). Although retrieval makes a memory vulnerable, reconsolidation during the labile period apparently strengthens the memory. Rats given several brief exposures to the training apparatus during the first few days after they learned a shock avoidance task showed no forgetting when tested 55 days after training (Inda, Muravieva, & Alberini, 2011).

Of course, there is no way to guarantee that reconsolidation will always be adaptive; the opportunity to correct errors also allows the introduction of new errors. We have long known that memories get "reconstructed" over time, usually by blending with other memories. Reconstruction can be a progressive affair. Evidence suggests that one reason for the "recovery" of *false* childhood memories during therapy may be therapists' repeated attempts to stimulate recall at successive sessions. Laboratory research has shown that people's agreement with memories planted by the experimenter can increase over multiple interviews (E. F. Loftus, 1997). In one study, researchers using doctored photographs found that after being questioned three times, 50% of subjects were describing a childhood ride in a hot air balloon that never happened (Wade, Garry, Read, & Lindsay, 2002). More recently, Loftus and her colleagues (D. M. Bernstein, Laney, Morris, & Loftus, 2005) were able to shift their subjects' food preferences by giving them a bogus computer analysis of their responses to a food questionnaire. For example, in a follow-up questionnaire, about 20% of the subjects agreed with the analysis that they had, in fact, been made sick by eating strawberry ice cream as children and reported that they would avoid it in the future.

CONCEPT CHECK

Take a Minute to Check Your Knowledge and Understanding

- Make a list of the changes that occur in neurons during learning.
- Describe LTP, LTD, and associative LTP.
- Consolidated memory is both stable and vulnerable. Explain.

Learning Deficiencies and Disorders

Learning may be the most complex of human functions. Not surprisingly, it is also one of the most frequently impaired. Learning can be compromised by accidents and violence that damage the structures we have been studying. But more subtle threats to learning ability come from aging and from disorders of the brain, including Alzheimer's disease and Korsakoff syndrome, which we will discuss in this section.

Effects of Aging on Memory

Old Man: Ah, memory. It's the second thing to go.

Young Man: So what's first?

Old Man: I forget . . .

You may or may not find humor in this old joke, but declining memory is hardly a laughing matter to the elderly. The older person might mislay car keys, forget appointments, or leave a pot on the stove for hours. Working memory and the ability to retrieve old memories and to make new memories may all be affected (Fahle & Daum, 1997; Small, Stern, Tang, & Mayeux, 1999). Although we usually associate aging with brain cell loss, significant deficits occur only in the midbrain, basal forebrain (lower frontal lobes), and some prefrontal areas. Some parts of the prefrontal cortex and hippocampus also decline in volume, likely due to a decrease in synaptic density. These areas, of course, are critical for learning, memory, and cognitive functioning (Mora, 2013).

Deficits occur at the molecular level as well. One study, for example, examined the brains of deceased individuals and found 17 genes in the dentate gyrus of the hippocampus that undergo changed levels of expression

with aging (Pavlopoulos et al., 2013). Downregulation of one of these genes results in less abundant production of the protein RbAp48 in humans and mice. This protein turns out to be important for memory: Young mice engineered to produce reduced RbAp48 showed dysfunction in the dentate gyrus and performed like old mice on memory tests. In the study described earlier, Genoux and his colleagues (2002) found that aged mice were significantly impaired on the learning task after just one day without practice, but performance in old mice with the enhanced PP1 inhibitor genes was still robust four weeks later. If we could find simple, safe ways to manipulate gene expression in humans, we could reduce many of the burdens of aging.

Some elderly people seem immune to the effects of aging on learning and cognition. Certainly, a part of this is genetic, but there have been many research efforts to identify environmental interventions that could benefit the rest of the population. Housing animals in an enriched environment reduces age-related changes in dendritic branching, neurogenesis, spine density, and cortical thickness; physical exercise and calorie restriction have similar effects in animals' brains and, in humans, improve cognitive functioning (Mora, 2013). We are beginning to appreciate the value of diet as well; consumption of fruits and vegetables containing flavonoids, for example, is associated with better language and episodic memory and slower cognitive decline in the elderly (Vauzour, 2014). In animals, flavonoids have been found to activate cellular learning mechanisms, enhance LTP, and increase hippocampal neurogenesis. There have been additional attempts to improve memory and general cognitive performance in the elderly through training, but these have not met with much success (Salthouse, 2006), despite the hype for commercial training programs. There could be many reasons for the lack of effect, including how meaningful and engaging the training tasks are and the amount of time spent in training. One promising effort is the Synapse Project, in which elderly individuals showed gains in episodic memory capabilities after spending 16 hours a week for three months learning digital photography or quilting, tasks that are both interesting and cognitively demanding (D. C. Park et al., 2014).

Alzheimer's Disease

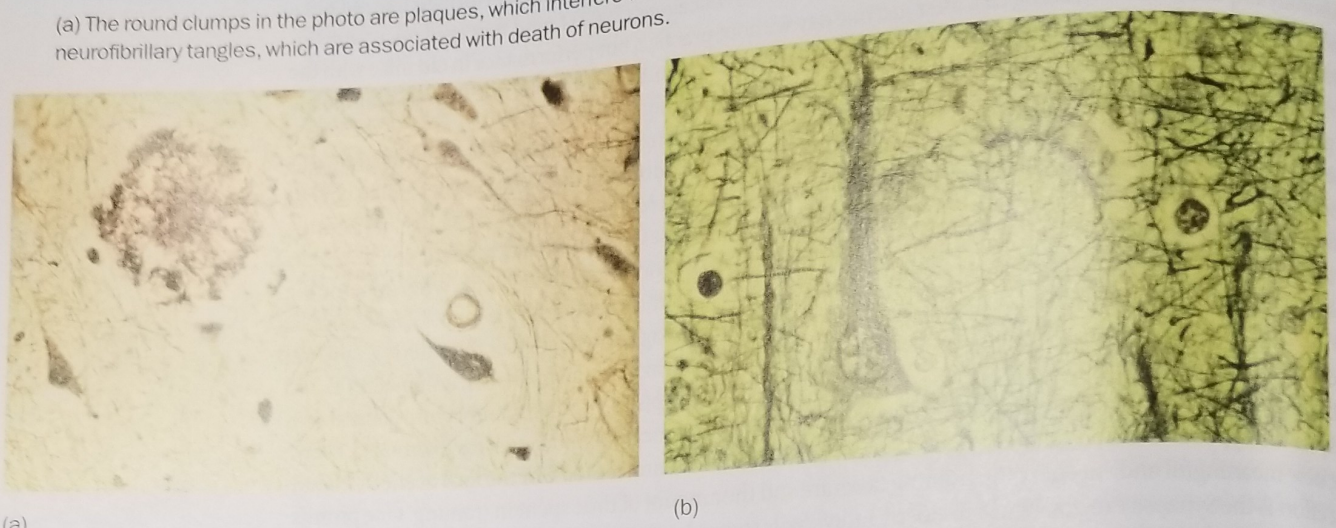
Substantial loss of memory and other cognitive abilities (usually, but not necessarily, in the elderly) is referred to as *dementia*. The most common cause of dementia is *Alzheimer's disease*, a disorder characterized by progressive brain deterioration and impaired memory and other cognitive abilities. Alzheimer's disease was first described by the neuroanatomist and neurologist Alois Alzheimer in 1906, after autopsying the brain of a 56-year-old patient with memory problems. Alzheimer's is primarily a disorder of the aged, but it can strike early in life. Of the nearly 5 million people in the United States with Alzheimer's, 4.7 million are over the age of 65 (Hebert, Weuve, Scherr, & Evans, 2013). The earliest and most severe symptom is usually impaired declarative memory. Initially, the person is indistinguishable from a normally aging individual, though the symptoms may start earlier; the person has trouble remembering events from the day before, mislays items, forgets names, and must search for the right word in a conversation. Later, the person repeats questions and tells the same story again during a conversation. As time and the disease progress, the person eventually fails to recognize acquaintances and even family members. Alzheimer's disease is not just a learning disorder but a disorder of the brain, so ultimately most behaviors suffer. Language, visual-spatial functioning, and reasoning are particularly affected, and there are often behavioral problems such as aggressiveness and wandering away from home. Alzheimer's researcher Zaven Khachaturian (1997) eloquently described his mother's decline: "The disease quietly loots the brain, nerve cell by nerve cell, like a burglar returning to the same house each night" (p. 21). Eventually, Alzheimer's is fatal; it is the sixth leading cause of death in the United States (S. L. Murphy, Xu, & Kochanek, 2013).

The Diseased Brain: Plaques and Tangles

There are two notable characteristics of the Alzheimer's brain, though they are not unique to the disease. *Plaques* are clumps of beta amyloid (Aβ), a type of protein, that cluster among axon terminals and interfere with neural transmission (Figure 12.16a). The main component is Aβ42, so called because it is 42 amino acids long; Aβ42 is particularly "sticky," so it clumps easily to form the plaques. In addition, abnormal accumulations of the protein tau form *neurofibrillary tangles* inside neurons; tangles are associated with the death of brain cells (Figure 12.16b). Plaques and tangles move through the brain in a predictable succession of stages, beginning with the medial cortex and progressing to the limbic areas, particularly the hippocampus, and then to the neocortex, the outer layers of cortex responsible for our highest functions (H. Braak & Braak, 1991). This accounts for the pattern of changing symptoms as the disease advances. Recently we've learned that this sequence parallels a progressive variation in two significant factors in those areas: the relative level of expression of inflammatory genes and the balance between proteins that promote or inhibit the aggregation (accumulation and clumping) of plaques and tangles (Figure 12.17; Freer et al., 2016). Interestingly, this differential

FIGURE 12.16 Neural Abnormalities in the Brain of a Person With Alzheimer's.

(a) The round clumps in the photo are plaques, which interfere with neural transmission. (b) The dark, twisted features are neurofibrillary tangles, which are associated with death of neurons.



(a) (b)

Sources: (a) © Dr. M. Goedert/Science Source. (b) © SPL/Science Source.

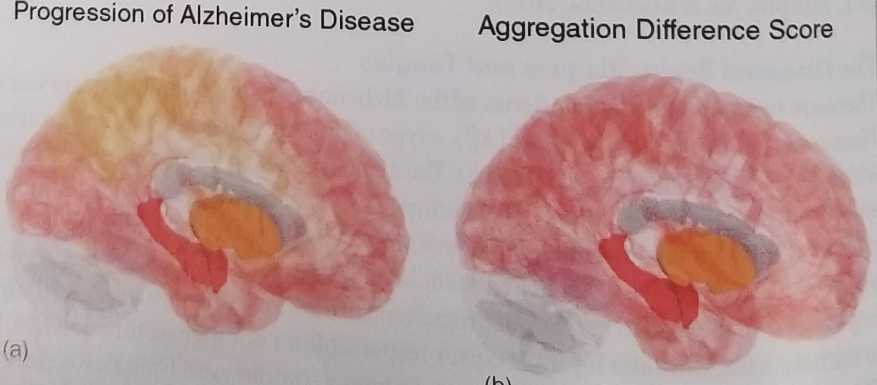
vulnerability among brain areas was discovered in healthy brains. Studying the progress of the disease can be difficult; we don't get a chance to look at the afflicted human brain until the disease is well advanced and, as the Research Spotlight explains, the laboratory models have been less than satisfactory.

Figure 12.18 compares the brain of a deceased Alzheimer's patient with a normal brain. Notice the decreased size of the gyri and the increased width of the sulci in the diseased brain. Internally, enlarged ventricles tell a similar story of severe neuron loss. Many of the lesions are in the temporal lobes; because of their location, they effectively isolate the hippocampus from its inputs and outputs, which partly explains the early memory loss (B. T. Hyman, Van Horsen, Damasio, & Barnes, 1984). However, plaques and tangles also attack the frontal lobes, accounting for additional memory problems as well as attention and motor difficulties. The occipital lobes and parietal lobes may be involved as well; disrupted communication between the primary visual area and the visual association areas in the parietal and temporal lobes explains the visual deficits that plague some Alzheimer's sufferers.

Although amyloid plaques have been considered the hallmark of Alzheimer's disease, the number of amyloid deposits is only moderately related to the degree of cognitive impairment (Selkoe, 1997), and about 25% of the elderly have plaques but suffer no dementia (Mintun et al., 2006). Researchers, however, are beginning to distinguish between insoluble forms of amyloid and soluble forms, which reach 70-fold higher levels in the brains of people with Alzheimer's (M. E. Larson & Lesné, 2012), and in mice have been linked

FIGURE 12.17 Alzheimer's Disease Progress Parallels Aggregation Difference Scores.

In (a), the darker the colors, the earlier plaques and tangles appear in that area; gray areas are unaffected. In (b), the darker the colors, the more aggregation promoters exceed aggregation-inhibiting proteins. Note the similarity in the images.



(a) (b)

Source: Excerpted from Figure 3 from "A Protein Homeostasis Signature in Healthy Brains Recapitulates Tissue Vulnerability to Alzheimer's Disease," by R. Freer, P. Sormanni, G. Vecchi, P. Ciryam, C. M. Dobson, & M. Vendruscolo, Science Advances, 2 (8), e1600947.

RESEARCH SPOTLIGHT

Alzheimer's in a Dish

Studying Alzheimer's disease in the laboratory has been difficult because the models used so far don't duplicate the pathology completely. Mice can be genetically engineered to produce the amyloid plaques, but not the neurofibrillary tangles; and cultures of neurons from Alzheimer's patients' brains produce amyloid and tau, but not the plaques and tangles. Researchers at Massachusetts General Hospital realized that the two-dimensional liquid cultures used in the laboratory are very different from the gelatinous environment of the brain, so they started using a three-dimensional gel to grow their cultures; to this they added stem cells that carried two gene variants known to cause Alzheimer's (S. H. Choi et al., 2014). After six weeks, the culture had both the typical amyloid and the toxic form of amyloid, and was complete with plaques and tangles. When they blocked the formation of plaques, they obtained the first direct evidence that plaque formation is a precursor to the development of the synapse-damaging tangles. The researchers say that the 3-D culture will allow them to screen hundreds of thousands of potential new drugs in a few months' time.

to memory failure, loss of synapses, and failure of LTP in the hippocampus (Gong et al., 2003). More recently we have learned that a modified form of tau, called *acetylated* tau (because of an added acetyl group), is particularly important because it depletes KIBRA, a protein required for inserting extra receptors into the neuronal membrane during learning (Tracy et al., 2016). Increasing KIBRA levels in cultured neurons reversed the effects of acetylated tau and restored their ability to strengthen connections, suggesting a new therapeutic approach.

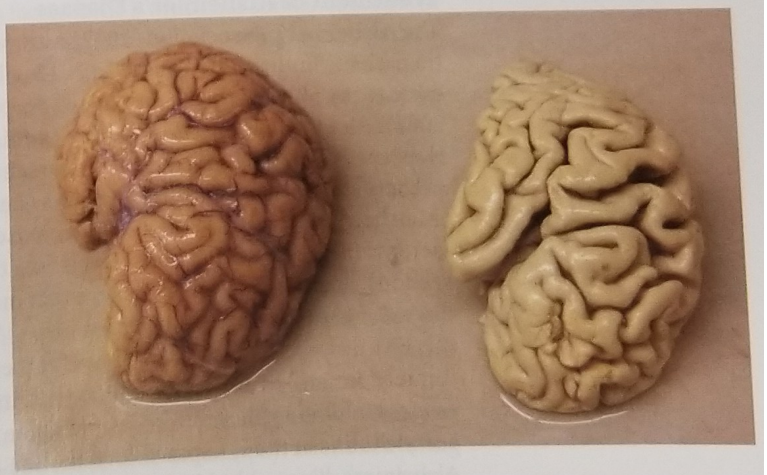
Heredity and Environment

Heredity is an important factor in Alzheimer's disease. The first clue to a gene location came from a comparison of Alzheimer's with Down syndrome (Lott, 1982). Down syndrome individuals also have plaques and tangles, and they invariably develop Alzheimer's disease if they live to the age of 50. Because Down syndrome is caused by an extra chromosome 21, researchers zeroed in on that chromosome; there they found mutations in the *amyloid precursor protein* (*APP*) gene (Goate et al., 1991). When aged mice were genetically engineered with an *APP* mutation that increased plaques, both LTP and spatial learning were impaired (Chapman et al., 1999). Three additional genes that influence Alzheimer's had been confirmed by the end of the 1990s; all of those affect amyloid production or its deposit in the brain (Selkoe, 1997). As you can see in Table 12.1, the genes fall into two classes, those associated with early-onset Alzheimer's disease (often before the age of 60) and one found in patients with late-onset Alzheimer's. The ε4 allele of the *APOE* gene is particularly interesting because it contributes to so many Alzheimer's cases. It increases risk by three- to eightfold and is associated with plaques and tangles, but how it contributes to pathology is not well understood. Two studies indicate that carriers without dementia have lower cerebral blood flow (Thambisetty, Beason-Held, An, Kraut, & Resnick, 2010) and that 2- to 25-month-old children with the allele have reduced growth in temporal and parietal areas, which are affected in patients with Alzheimer's (Dean et al., 2014).

The four genes in the table account for just a little over half the cases of Alzheimer's disease, so there are likely many rare or small-effect genes as well as environmental influences. Discovery of additional genes had to await whole-genome studies with large numbers

FIGURE 12.18 Normal Brain (Left) and Alzheimer's Brain

The illustration shows the most obvious differences, the reduced size of gyri and increased size of sulci produced by cell loss in the diseased brain.



Source: REUTERS/Denis Balibouse.

TABLE 12.1 Known Genes for Alzheimer's Disease.

GENE	CHROMOSOME	AGE OF ONSET (YEARS)	PERCENTAGE OF CASES
APP	21	45–66	<0.1
Presenilin 1	14	28–62	1–2
Presenilin 2	1	40–85	<0.1
ApoE4	19	>60	>50

Sources: Marx (1998); Selkoe (1997).

of individuals. Such studies have the advantage that they allow gene searches without the need for a preconceived target area. Prior to 2009, 11 genes had been associated with Alzheimer's, but a whole-genome study of 74,000 individuals was able to add 11 additional gene locations (Lambert et al., 2013). Although the genes themselves have not been identified yet, genes near the loci are involved in amyloid and tau pathways, inflammation, immune response, cell migration, and cellular functions.

Genome-wide studies have also made it possible to do broad searches for epigenetic changes, and in the past few years the focus has been shifting in that direction. A recent study conclusively identified seven genes that were differentially methylated in Alzheimer's patients by taking the unusual step of verifying their results in a second group of subjects (De Jager et al., 2014). If we could identify the environmental conditions that trigger these changes, then preventive measures could reduce the incidence of Alzheimer's. A meta-analysis identified several environmental risks for dementia, including exposure to pesticides, fertilizers, herbicides, and insecticides; airborne particulate matter; second-hand smoke; and electromagnetic fields (Killin, Starr, Shiue, & Russ, 2016). On the health side, we can add vitamin D deficiency (Killin et al.), sedentary lifestyle, diabetes, obesity, smoking, and hypertension (Baumgart et al., 2015). In addition, studies with combat soldiers, football players, and boxers have established a strong link between traumatic brain injury and Alzheimer's-like brain pathology and dementia (Vincent, Roebuck-Spencer, & Cernich, 2014). A meta-analysis found a 5-fold increase in Alzheimer's disease with *Chlamydophila pneumoniae* bacterial infection and a 10-fold increase with spirochete infection (Maheshwari & Eslick, 2015). Indeed, there is increasing evidence that beta amyloid can be triggered by infection and acts as an antimicrobial agent; in the first study in living models, human beta amyloid protected human neural cells from *Candida* infection and round-worms from infection by *Candida* and *Salmonella,* and significantly extended the survival time of mice after *Salmonella* infection (Kumar et al., 2016).

Treatment of Alzheimer's Disease

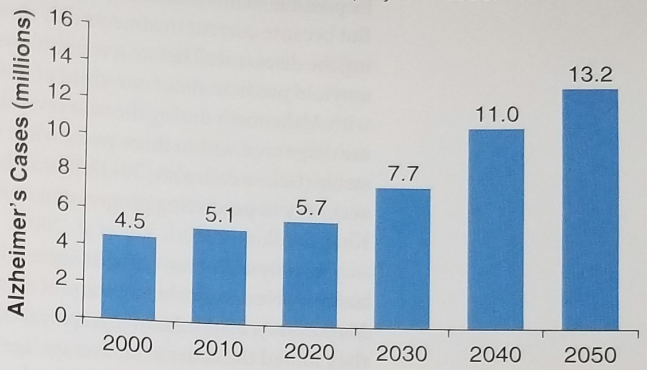
The Alzheimer's Association (2017) estimates that the cost of caring for Alzheimer's and other dementia patients in the United States in 2017 will be $259 billion. By 2050, the U.S. population is expected to increase by 50%, while the number of people over the age of 85 increases sixfold (Bureau of the Census, 2001). As a result, experts have been predicting that Alzheimer's rates will almost triple (Figure 12.19; Hebert et al., 2013. In the past few years, however, at least nine studies have shown a declining risk for Alzheimer's in the wealthiest nations (Langa, 2015), including a 20% drop in the United Kingdom (Matthews et al., 2015) and a 26% decrease in the United States (Langa et al., 2017). One contributing factor is increasing educational levels (see the discussion of the cognitive reserve hypothesis in the next section), and the researchers believe that more effective treatment of health risks such as cardiovascular disease make up the rest of the difference.

Five drugs are currently approved for the treatment of Alzheimer's in the United States, but one of those is rarely prescribed due to side effects (Patoine & Bilanow, n.d.). Three of the ones in regular use are cholinesterase inhibitors; they restore acetylcholine transmission by interfering with the enzyme that breaks down acetylcholine at the synapse. Acetylcholine-releasing neurons are significant victims of degeneration in Alzheimer's disease; blocking acetylcholine activity impairs learning in humans (Newhouse, Potter, Corwin, &

Lenox, 1992), and in rats it interferes with learning by eliminating hippocampal theta (J. A. Deutsch, 1983), rhythmic neural activity that is necessary for LTP to occur. The fourth drug, memantine (marketed in the United States as Namenda), was the first approved for use in patients with moderate and severe symptoms. Some of the neuron loss in Alzheimer's occurs when dying neurons trigger the release of the excitatory transmitter glutamate; the excess glutamate produces excitotoxicity, overstimulating NMDA receptors and killing neurons. Memantine limits the neuron's sensitivity to glutamate, reducing further cell death. Studies indicate moderate slowing of deterioration and improvement in symptoms (Reisberg et al., 2003; U.S. Food and Drug Administration, 2003). Unfortunately, these drugs provide only modest relief for the memory and behavioral symptoms of Alzheimer's, and they are little or no help when degeneration is advanced.

FIGURE 12.19 Projected Increases in Alzheimer's Disease in the United States.

Note that numbers begin to escalate rapidly after 2020.



Source: Based on data from Hebert et al. (2013).

In their quest for more effective treatments, researchers are mounting efforts on three major fronts: removing beta amyloid or blocking its formation, preventing tau from forming tangles, and reducing inflammation. However, no new drug has been approved by the FDA since 2003, and the disappointments continue to accumulate. The failure of two large trials of anti-amyloid antibodies, one of which was at the final phase 3 level, has some researchers now thinking that once symptoms have appeared the treatment is too late; they are shifting to pretreatment in asymptomatic individuals who are at genetic risk (Callaway, 2012). Similarly, a phase 3 trial attempting to treat inflammation with injections of immunoglobulin has come up empty-handed (Weill Cornell Medical College, 2014). However, the tangle-preventing drug LMTX is now in phase 3 clinical trials, after reducing symptom progression by 90% in phase 2 trials (TauRx Therapeutics, n.d.).

Stem cell and gene therapy are obvious treatment possibilities, and although work is in the early stages, progress is being made. A Florida stem cell research company has a phase 1 human safety trial under way; if nothing else, the researchers expect benefits from the anti-inflammatory effects of stem cells (Stem Cells Portal, 2017). On the gene therapy front, a Chinese team has demonstrated that neural stem cells can be used to deliver RNA to silence the gene responsible for the key enzyme in beta amyloid production (Z. Liu et al., 2013); in the United States, researchers have increased axonal sprouting among degenerating neurons by inserting a gene for nerve growth factor into patients' brains (Tuszynski et al., 2015). *Brain-derived neurotrophic factor (BDNF)* prevents the death of neurons and stimulates their functioning; individuals with the highest levels of BDNF were 33% less likely to develop dementia and Alzheimer's disease than those with the lowest levels (G. Weinstein et al., 2014). BDNF is in phase 1 clinical trials; and nerve growth factor (NGF), which has similar effects, is in phase 2 trials (Tuszynski & Nagahara, 2016). Researchers also continue to focus on removing plaques from the brain. After much promise from animal studies and multiple failures with humans, one drug (aducanumab) has been successful in reducing both soluble and insoluble beta amyloid and slowing cognitive decline; the drug is now in phase 3 trials (Sevigny et al., 2016). Another approach showing promise in animals is ultrasound stimulation of the brain; it cleared plaques in the brains of mice engineered to duplicate some characteristics of Alzheimer's, apparently by stimulating glia to ingest the plaques, resulting in reversal of lost memory capability (Leinenga & Götz, 2015).

Detecting Alzheimer's Disease

The aging individual dealing with memory problems typically wonders "Am I getting Alzheimer's?" No single test can diagnose Alzheimer's, but a battery of physical, neurological, and cognitive tests can do a reasonably good job, mostly by ruling out other forms of dementia that may be more treatable, if not reversible. The physician may also order an MRI to look for atrophy in the temporal and parietal areas. For many years, patients were told that a definite diagnosis could be made only on autopsy, after examining the brain for plaques and tangles, but recent advances in PET scanning and measurement of biomarkers is