Unlike most other forms of conditioning, taste aversion develops even when the unconditioned response (poison-induced nausea) occurs after a long delay, up to hours after the CS (specific taste). This makes biological sense because the ill effects of infected foods and naturally occurring toxins usually follow ingestion only after some delay. For most species, including humans, taste-aversion conditioning occurs only when certain tastes are associated with illness. Taste aversion develops poorly if a taste is followed by a painful stimulus that does not produce nausea. Also, animals do not develop an aversion to a visual or auditory stimulus that has been paired with nausea.

Errors and Imperfections in Memory Shed Light on Normal Memory Processes

Memory allows us to revisit our personal past; provides access to a vast network of facts, associations, and concepts; and supports learning and adaptive behavior. But memory is not perfect. We often forget events rapidly or gradually, sometimes distort the past, and occasionally remember events that we would prefer to forget. In the 1930s, the British psychologist Frederic Bartlett reported experiments in which people read and tried to remember complex stories. He showed that people often misremember many features of the stories, often distorting information based on their expectations of what should have happened. Forgetting and distortion can provide important insights into the workings of memory.

Memory's imperfections have been classified into seven basic categories, dubbed the "seven sins of memory": transience, absent-mindedness, blocking, misattribution, suggestibility, bias, and persistence. Here, we focus on six of these.

Absent-mindedness results from a lack of attention to immediate experience. Absent-mindedness during encoding is a likely source of common memory failures such as forgetting where one recently placed an object. Absent-mindedness also occurs when we forget to carry out a particular task such as picking up groceries on the way home from the office, even though we initially encoded the relevant information.

Blocking refers to a temporary inability to access information stored in memory. People often have partial awareness of a sought-after word or image but are nonetheless unable to recall the entire word accurately or completely. Sometimes, it feels like a blocked word is on "the tip of the tongue"—we are aware of the initial letter of the word, the number of syllables in it, or a like-sounding word. Determining which information is correct and which is incorrect requires a great deal of conscious effort.

Absent-mindedness and blocking are sins of omission: At a moment when we need to remember information, it is inaccessible. However, memory is also characterized by sins of commission, situations in which some form of memory is present but wrong.

Misattribution refers to the association of a memory with an incorrect time, place, or person. False recognition, a type of misattribution, occurs when individuals report that they "remember" items or events that never happened. Such false memories have been documented in controlled experiments where people claim to have seen or heard words or objects that had not been presented previously but are similar in meaning or appearance to what was actually presented. Studies using positron emission tomography imaging and fMRI have shown that many brain regions show similar levels of activity during both true and false recognition, which may be one reason why false memories sometimes feel like real ones.

Suggestibility refers to the tendency to incorporate new information into memory, usually as a result of leading questions or suggestions about what may have been experienced. Research using hypnotic suggestion indicates that various kinds of false memories can be implanted in highly suggestible individuals, such as remembering hearing loud noises at night. Studies with young adults have also shown that repeated suggestions about a childhood experience can produce memories of events that never occurred. These findings are important theoretically because they highlight that memory is not simply a "playback" of past experiences (Box 52–1). Despite these important theoretical and practical implications, next to nothing is known about the neural bases of suggestibility.

Bias refers to distortions and unconscious influences on memory that reflect one's general knowledge and beliefs. People often misremember the past to make it consistent with what they presently believe, know, or feel. This idea is consistent with the idea of "predictive coding" supported by studies showing that even low-level neural mechanisms of perception and sensation are shaped by expectations. The specific brain mechanisms by which expectations influence memory are not well understood.

Persistence refers to obsessive memory, constant remembering of information or events that we might want to forget. Neuroimaging studies have illuminated some neurobiological factors that contribute to persistent emotional memories. Some key results implicate the amygdala, the almond-shaped structure near the hippocampus long known to be involved in emotional

processing (Chapter 42). Studies indicate that the level of recall of emotional components of a story is correlated with the level of activity in the amygdala during presentation of the story. Related studies implicate the amygdala in the encoding and retrieval of emotionally charged experiences that can repeatedly intrude into consciousness.

Although persistence can be disabling, it also has adaptive value. The persistence of memories of disturbing experiences increases the likelihood that we will recall information about arousing or traumatic events at times when it may be crucial for survival.

Indeed, many memory imperfections may have adaptive value. False memories and suggestibility may both be related to one of the most basic adaptive functions of memory: the integration of experiences separated in time into a network of learned associations. For memory to play an important role in guiding future behavior, it must be flexible so that we can leverage past experiences to make inferences about future events even when the circumstances have changed. Similarly, although the various forms of forgetting (transience, absent-mindedness, and blocking) can be annoying, a memory system that automatically retains every detail of every experience could result in an overwhelming clutter of useless trivia. This is exactly what happened in the fascinating case of Shereshevski, a mnemonist studied by the Russian neuropsychologist Alexander Luria and described in the book *The Mind of a Mnemonist*. Shereshevski was filled with highly detailed memories of his past experiences but was unable to generalize or to think at an abstract level. A healthy memory system does not encode, store, and retrieve all the details of every experience. Thus, transience, absent-mindedness, and blocking allow us to avoid the unfortunate fate of Shereshevski.

Highlights

1. Different forms of learning and memory can be distinguished behaviorally and neurally. Working memory maintains goal-relevant information for short periods. Explicit (or declarative) memory involves two classes of knowledge: episodic memory, which represents personal experiences, and semantic memory, which represents general knowledge and facts. Implicit memory includes forms of perceptual and conceptual priming, as well as the learning of motor and perceptual skills, perceptual regularities, and reinforced habits.
2. Encoding, storage, retrieval, and consolidation of new explicit memories depend on interactions between specific regions within the neocortex and medial temporal lobe and specific hippocampal subregions. The initiation of long-term storage of explicit memory requires the temporal lobe system, as highlighted by studies of amnesic patients such as H.M. Consolidation processes stabilize stored representations, rendering explicit memories less dependent on the medial temporal lobe. Retrieval of explicit memories involves the medial temporal lobe, as well as frontoparietal networks that subserve attention and cognitive control.
3. Multiple processes interact to support memory-guided behavior. Retrieval of episodic memory guides the imagining of future events, which is important for making decisions about future choices and actions. Motivationally significant events are prioritized in memory through the enhancement of encoding, storage, and consolidation processes. Motivation also impacts retrieval, perhaps through different mechanisms of prioritization.
4. Implicit memory emerges automatically in the course of perceiving, thinking, and acting. It tends to be inflexible and expressed in the performance of tasks even without conscious awareness. Implicit memory involves a wide variety of brain regions and circuits, including cortical areas that support the specific perceptual, conceptual, or motor systems recruited to process a stimulus or perform a task, as well as the striatum and the amygdala. Implicit learning that involves the encoding of relational associations additionally involves the hippocampus.
5. Imperfections and errors in remembering provide telltale clues about learning and memory mechanisms. The past can be forgotten or distorted, indicating that memory is not a faithful record of all details of every experience. Retrieved memories are the result of a complex interplay among various brain regions and can be reshaped over time by multiple influences. Various forms of forgetting and distortion tell us much about the flexibility of memory that allows the brain to adapt to the physical and social environment.

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53

Cellular Mechanisms of Implicit Memory Storage and the Biological Basis of Individuality

Throughout this book we have emphasized that all behavior is a function of the brain and that malfunctions of the brain produce characteristic disturbances of behavior. Behavior is also shaped by experience. How does experience act on the neural circuits of the brain to change behavior? How is new information acquired by the brain, and once acquired, how is it stored, retrieved, and remembered?

In the previous chapter, we saw that memory is not a single process but has at least two major forms. Implicit memory operates unconsciously and automatically, as in the memory for conditioned responses, habits, and perceptual and motor skills, whereas explicit memory operates consciously, as in the memory for people, places, and objects. The circuitry for long-term memory storage differs between explicit and implicit memory. Long-term storage of explicit memory begins in the hippocampus and the medial temporal lobe of the neocortex, whereas long-term storage of different types of implicit memory requires a family of neural structures: the neocortex for priming, the striatum for skills and habits, the amygdala for Pavlovian threat conditioning (also known as fear conditioning), the cerebellum for learned motor skills, and certain reflex pathways for nonassociative learning such as habituation and sensitization (Figure 53–1).

Over time, explicit memories are transferred to different regions of the neocortex. In addition, many cognitive, motor, and perceptual skills that we initially store as explicit memory ultimately become so ingrained with practice that they become stored as implicit memory. The transference from explicit to implicit memory and the difference between them is dramatically demonstrated in the case of the English musician and conductor Clive Waring, who in 1985 sustained a viral infection of his brain (herpes encephalitis) that affected

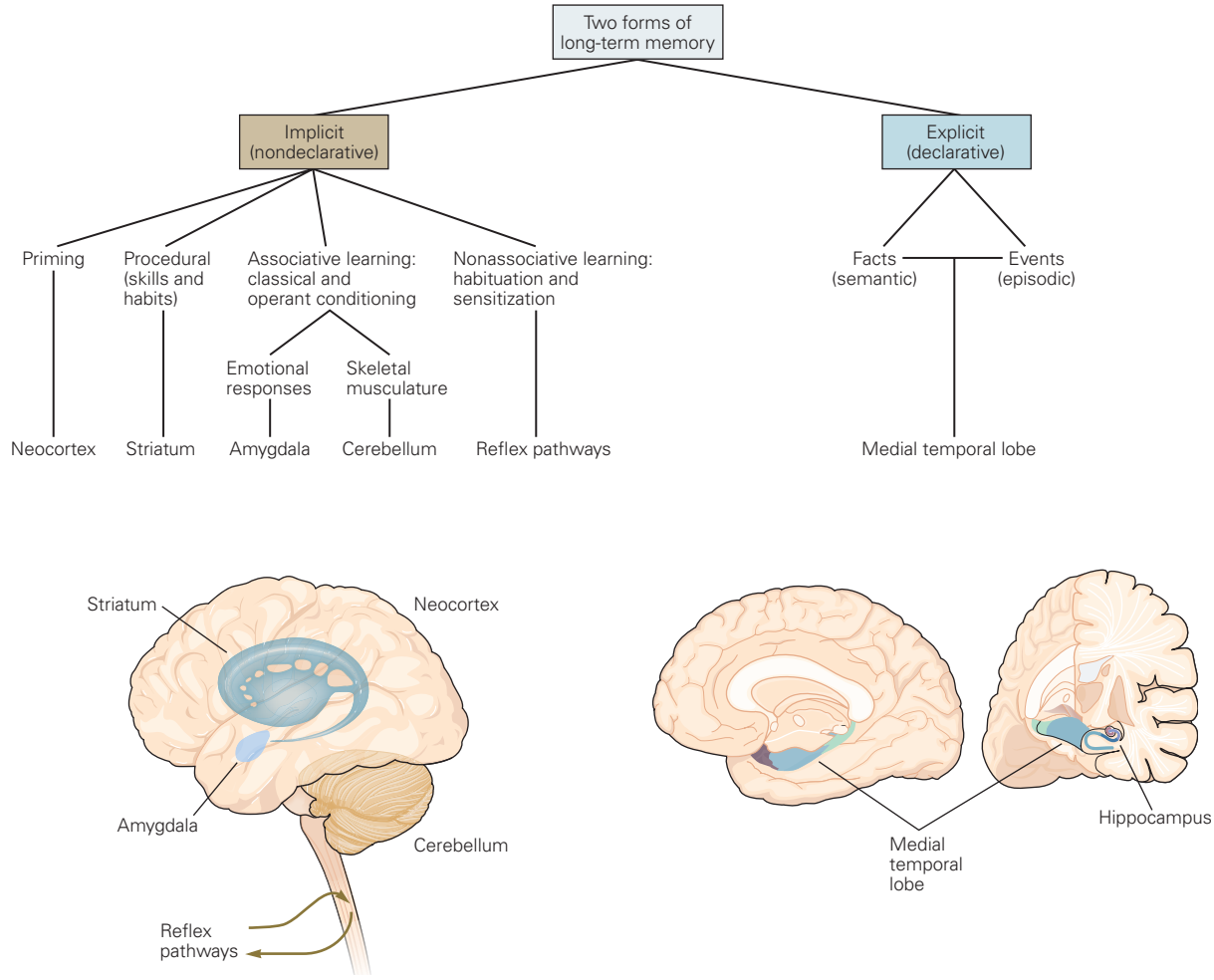

Figure 53–1 Two forms of long-term memory involve different brain systems. Implicit memory involves the neocortex, striatum, amygdala, cerebellum, and, in the simplest cases, the reflex pathways themselves. Explicit memory requires the medial temporal lobe and the hippocampus, as well as certain areas of neocortex (not shown).

the hippocampus and temporal cortex. Waring was left with a devastating loss of memory for events or people he had encountered even a minute or two earlier, but his ability to read music, play the piano, or conduct a chorale was unaffected. Once a performance was completed, however, he could not remember a thing about it.

Similarly, the abstract expressionist painter William de Kooning developed severe disturbances of explicit memory as a result of Alzheimer disease. As the disease progressed and his memory for people, places, and objects deteriorated, he nevertheless continued to produce important and interesting paintings. This aspect of his creative personality was relatively untouched.

In this chapter, we examine the cellular and molecular mechanisms that underlie implicit memory storage in invertebrate and vertebrate animals. We focus on learning about threats (sometimes called fear learning). Implicit memory for motor skills and habits in mammals involving the cerebellum and basal ganglia was considered in Chapters 37 and 38. In the next chapter, we examine the biology of explicit memory in mammals.

Storage of Implicit Memory Involves Changes in the Effectiveness of Synaptic Transmission

Studies of elementary forms of implicit learning—habituation, sensitization, and classical conditioning—provided the conceptual framework for investigating the neural mechanisms of memory storage. Such learning has been analyzed in simple invertebrates and in a variety of vertebrate behaviors, such as the flexion and

eye blink reflexes, and also defensive behaviors such as freezing. These simple forms of implicit memory involve changes in the effectiveness of the synaptic pathways that mediate the behavior.

Habituation Results From Presynaptic Depression of Synaptic Transmission

Habituation is the simplest form of implicit learning. It occurs, for example, when an animal learns to ignore a novel stimulus. An animal reacts to a new stimulus with a series of orienting responses. If the stimulus is neither beneficial nor harmful, the animal learns to ignore it after repeated exposure.

The physiological basis of this behavior was first investigated by Charles Sherrington while studying posture and locomotion in cats. Sherrington observed a decrease in the intensity of certain reflexes in response to repeated electrical stimulation of the motor pathways. He suggested that this decrease, which he called *habituation*, is caused by diminished synaptic effectiveness in the stimulated pathways.

Habituation was later investigated at the cellular level by Alden Spencer and Richard Thompson. They found close cellular and behavioral parallels between habituation of a spinal flexion reflex in cats (the withdrawal of a limb from a noxious stimulus) and habituation of more complex human behaviors. They showed that during habituation the strength of the input from local excitatory interneurons onto motor neurons in the spinal cord decreased, whereas the input to the same interneurons from sensory neurons innervating the skin was unchanged.

Because the organization of interneurons in the vertebrate spinal cord is quite complex, it was difficult to analyze further the cellular mechanisms of habituation in the flexion reflex. Progress required a simpler system. The marine mollusk *Aplysia californica*, which has a simple nervous system of about 20,000 central neurons, proved to be an excellent system for studying implicit forms of memory.

Aplysia has a repertory of defensive reflexes for withdrawing its respiratory gill and siphon, a small fleshy spout above the gill used to expel seawater and waste (Figure 53–2A). These reflexes are similar to the withdrawal reflex of the leg studied by Spencer and Thompson. Mild touching of the siphon elicits reflex withdrawal of both the siphon and gill. With repeated stimulation, these reflexes habituate. As we shall see, these responses can also be dishabituated, sensitized, and classically conditioned.

The neural circuit mediating the gill-withdrawal reflex in *Aplysia* has been studied in detail. Touching the siphon excites a population of mechanoreceptor sensory neurons that innervate the siphon. The release of glutamate from sensory neuron terminals generates fast excitatory postsynaptic potentials (EPSPs) in interneurons and motor cells. The EPSPs from the sensory cells and interneurons summate on motor cells both temporally and spatially, causing them to discharge strongly, thereby producing vigorous withdrawal of the gill. If the siphon is repeatedly touched, however, the monosynaptic EPSPs produced by sensory neurons in both interneurons and motor cells decrease progressively, paralleling the habituation of gill withdrawal. In addition, repeated stimulation also leads to a decrease in the strength of synaptic transmission from the excitatory interneurons to the motor neurons; the net result is that the reflex response diminishes (Figure 53–2B,C).

What reduces the effectiveness of synaptic transmission between the sensory neurons and their postsynaptic cells during repeated stimulation? Quantal analysis (Chapter 15) revealed that the amount of synaptic glutamate released from presynaptic terminals of sensory neurons decreases. That is, fewer synaptic vesicles are released with each action potential in the sensory neuron; the sensitivity of the postsynaptic glutamate receptors does not change. Because the reduction in transmission occurs in the activated pathway itself and does not require another modulatory cell, the reduction is referred to as *homosynaptic depression*. This depression lasts many minutes.

An enduring change in the functional strength of synaptic connections thus constitutes the cellular mechanism mediating short-term habituation. As change of this type occurs at several sites in the gill-withdrawal reflex circuit, *memory is distributed and stored throughout the circuit*. Depression of synaptic transmission by sensory neurons, interneurons, or both is a common mechanism underlying habituation of escape responses of crayfish and cockroaches as well as startle reflexes in vertebrates.

How long can the effectiveness of a synapse change last? In *Aplysia*, a single session of 10 stimuli leads to short-term habituation of the withdrawal reflex lasting minutes. Four sessions separated by periods ranging from several hours to 1 day produce long-term habituation, lasting as long as 3 weeks (Figure 53–3).

Anatomical studies indicate that long-term habituation is caused by a decrease in the number of synaptic contacts between sensory and motor neurons. In naïve animals, 90% of the sensory neurons make physiologically detectable connections with identified motor neurons. In contrast, in animals trained for

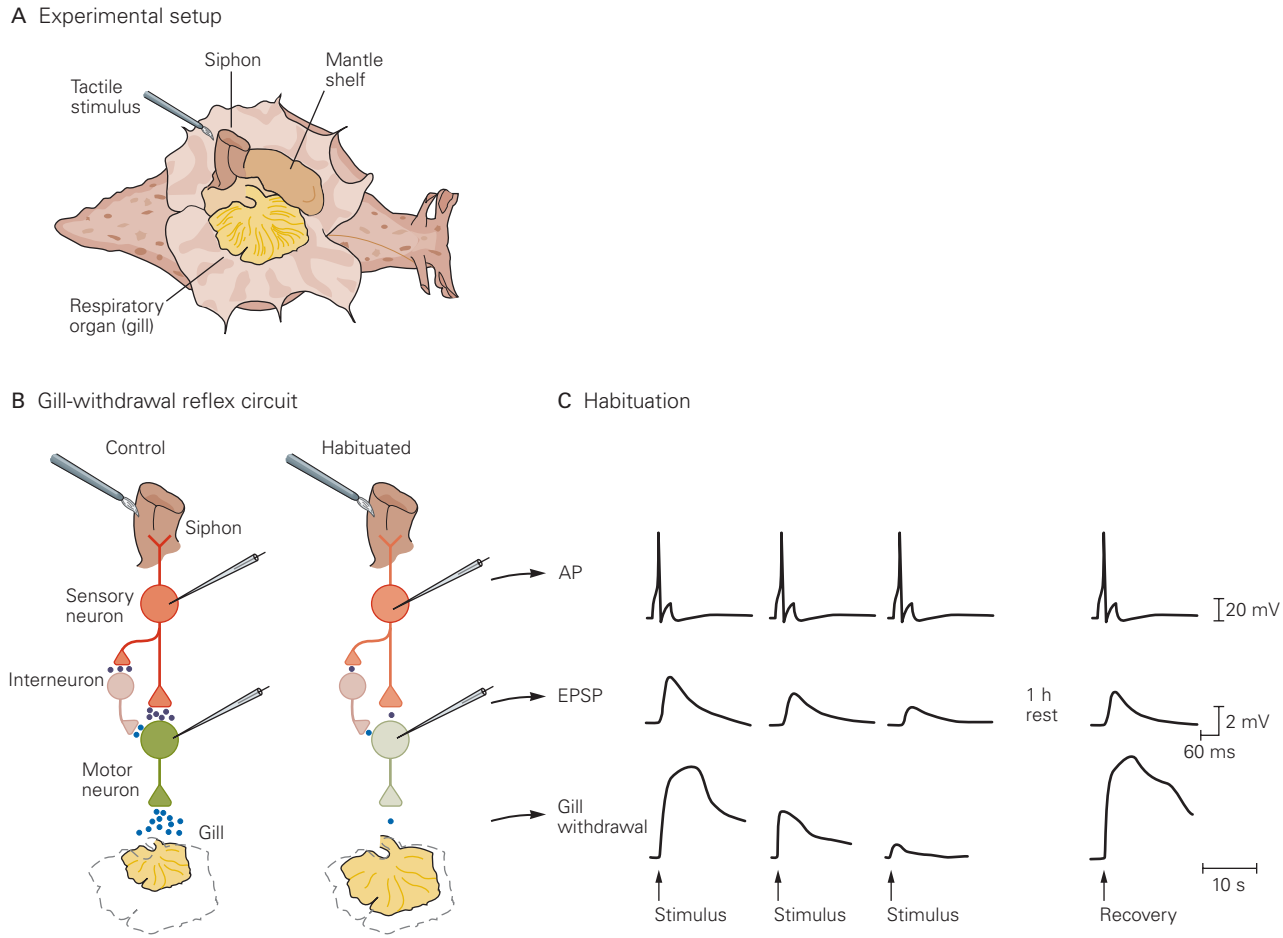

Figure 53–2 Short-term habituation of the gill-withdrawal reflex of the marine snail *Aplysia*.

A. A dorsal view of *Aplysia* illustrates the respiratory organ (gill) and the mantle shelf, which ends in the siphon, a fleshy spout used to expel seawater and waste. Touching the siphon elicits the gill-withdrawal reflex. Repeated stimulation leads to habituation.

B. Simplified diagrams of the gill-withdrawal reflex circuit and sites involved in habituation. Approximately 24 mechanoreceptor neurons in the abdominal ganglion innervate the siphon skin. These sensory cells make excitatory synapses onto a cluster of six motor neurons that innervate the gill, as well as on interneurons that modulate the firing of the motor neurons. (For simplicity, only one of each type of neuron is illustrated here.) Touching the siphon leads to withdrawal of the gill (**dashed outline** shows original gill size; **solid outline** shows maximal withdrawal).

C. Repeated stimulation of the siphon sensory neuron (**top traces**) leads to a progressive depression of synaptic transmission between the sensory and motor neurons. The size of the motor neuron excitatory postsynaptic potential (**EPSP**) gradually decreases despite no change in the presynaptic action potential (**AP**). In a separate experiment, repeated stimulation of the siphon results in a decrease in gill withdrawal (habituation). One hour after repetitive stimulation, both the EPSP and gill withdrawal have recovered. Habituation involves a decrease in transmitter release at many synaptic sites throughout the reflex circuit. (Adapted, with permission, from Pinsker et al. 1970; Castellucci and Kandel 1974.)

long-term habituation, the incidence of connections is reduced to 30%; the reduction in number of synapses persists for a week and does not fully recover even 3 weeks later (see Figure 53–9). As we shall see, the converse occurs with long-term sensitization, where synaptic transmission is associated with an *increase* in the number of synapses between sensory and motor neurons.

Not all classes of synapses are equally modifiable. In *Aplysia*, the strength of some synapses rarely changes, even with repeated activation. In synapses specifically involved in learning (such as the connections between sensory and motor neurons in the withdrawal reflex circuit), a relatively small amount of training can produce large and enduring changes in synaptic strength.

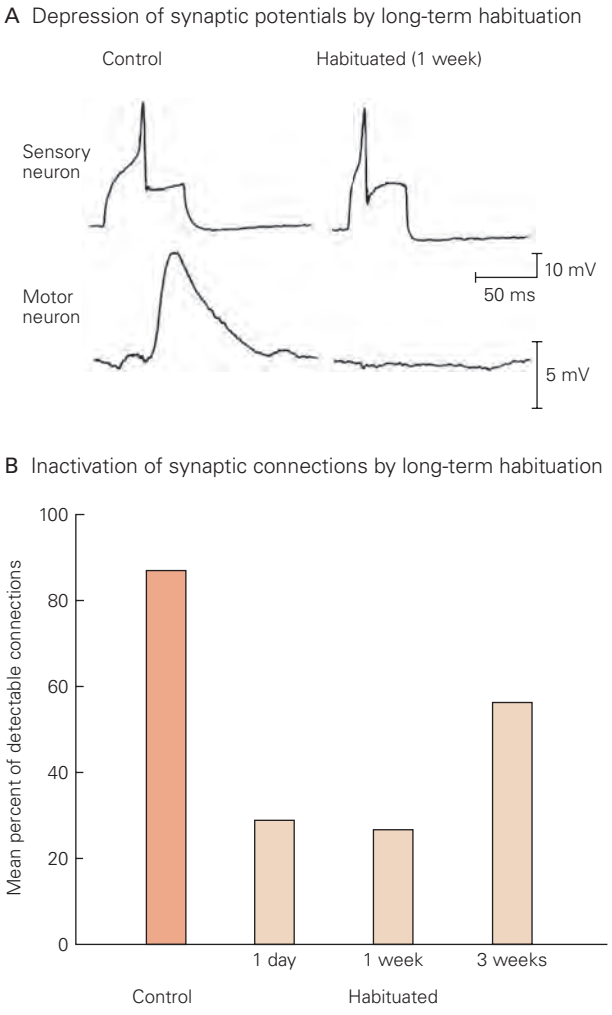

Figure 53–3 Long-term habituation of the gill-withdrawal reflex in *Aplysia.* (Adapted, with permission, from Castellucci, Carew, and Kandel 1978.)

A. Comparison of action potentials in sensory neurons and the postsynaptic potential in motor neurons in an untrained animal (control) and one that has been subjected to long-term habituation. In the habituated animal 1 week after training, no synaptic potential occurs in the motor neuron in response to the sensory neuron action potential.

B. After long-term habituation training, the mean percentage of sensory neurons making physiologically detectable connections with motor neurons is reduced even at 3 weeks.

Sensitization Involves Presynaptic Facilitation of Synaptic Transmission

The ability to recognize and respond to danger is necessary for survival. Not only snails and flies, but all animals, including humans, must distinguish predators from prey and hostile environments from safe ones. Because the ability to respond to threats is a universal requirement of survival, it has been conserved throughout evolution, allowing studies of invertebrates to shed light on neural mechanisms in mammals.

At the beginning of the 20th century, both Freud and Pavlov appreciated that anticipatory defensive responses to danger signals are biologically adaptive, a fact that likely accounts for the profound conservation of this capacity throughout vertebrates and invertebrates. In the laboratory, threat (fear) conditioning is typically studied by presenting a neutral stimulus, such as a tone, prior to the onset of an aversive stimulus, such as electrical shock. The two stimuli become associated such that the tone leads to the elicitation of defensive behaviors that protect against the harmful consequences predicted by the tone. Freud called this "signal anxiety," which prepares the individual for fight or flight when there is even the suggestion of external danger.

When an animal repeatedly encounters a harmless stimulus, its responsiveness to the stimulus habituates, as seen above. In contrast, when the animal confronts a *harmful* stimulus, it typically learns to respond more vigorously to a subsequent presentation of the same stimulus. Presentation of a harmful stimulus can even cause an animal to mount a defensive response to a subsequent *harmless* stimulus. As a result, defensive reflexes for withdrawal and escape become heightened. This enhancement of reflex responses is called *sensitization.*

Like habituation, sensitization can be transient or long lasting. A single shock to the tail of an *Aplysia* produces short-term sensitization of the gill-withdrawal reflex that lasts minutes; five or more shocks to the tail produce sensitization lasting days to weeks. Tail shock is also sufficient to overcome the effects of habituation and enhance a habituated gill-withdrawal reflex, a process termed *dishabituation*.

Sensitization and dishabituation result from an enhancement in synaptic transmission at several connections in the neural circuit of the gill-withdrawal reflex, including the connections made by sensory neurons with motor neurons and interneurons—the same synapses depressed by habituation (Figure 53–4A). Typically, modifiable synapses can be regulated bidirectionally, participate in more than one type of learning, and store more than one type of memory. The bidirectional synaptic changes that underlie habituation and sensitization are the result of different cellular mechanisms. In *Aplysia*, the same synapses that are weakened by habituation through a homosynaptic process can be strengthened by sensitization through a *heterosynaptic* process that depends on modulatory