In 1910, the French philosopher Henri Bergson wrote about what we now call nondeclarative memory. Focusing especially on habits, he wrote, "[It is] a memory profoundly different . . . always bent upon action, seated in the present and looking only to the future. . . . In truth it no longer represents our past to us, it acts it; and if it still deserves the name of memory, it is not because it conserves bygone images, but because it prolongs their useful effect into the present moment."

When we are introduced to a visitor, we extend our hand in greeting. We can look at the sky on a cloudy day and have some idea about the likelihood of rain. When we read as adults, we execute a complex skill of eye movements and text comprehension that has been improved during thousands of hours of practice. How reliably or accurately we do these things depends on our past experience and on the opportunities we have had for instruction and practice. But we do learn, and we come to perform these and countless other tasks without being aware that we are using memory. In this final chapter on nondeclarative memory, we consider examples of skill learning, habit learning, and classical conditioning. These extend the discussion of nondeclarative memory in earlier chapters and illustrate its pervasive influence in everyday life.
**Motor Skills**

As we noted in Chapter 1, the first hint that memory in the brain is organized into separate systems came from studies of motor skill learning. Patient H.M., though profoundly amnesic for facts and events and ordinary remembering, nevertheless learned to trace the outline of a star in a mirror. Skill learning of this kind has always been easy to understand intuitively as something special, different from the ordinary remembering of recent events. For example, when we learn a forehand in tennis, it seems reasonable to suppose that demonstrating our improved tennis swing is fundamentally different from remembering the tennis lessons themselves or remembering the time we used a forehand to win a particular match.

Our intuitions about motor skills and perceptual-motor skills are quite correct. Learned skills are embedded in procedures, which can be expressed through performance. They are not declarative: one does not need to "declare" anything, and one may not be able to say very much about what one is doing, even when pressed. Indeed, experience shows that trying to express conscious knowledge about a motor skill while performing it is a good way to impair its execution.

We can learn a motor skill without having any awareness at all of what is being learned. This curious unconscious learning process has been well demonstrated in studies of a form of motor skill learning called sequence learning. In the best-studied example of this type of learning, which also includes a perceptual component, individuals make rapid keypresses in response to a visual signal that appears sequentially in one of four locations on a screen (A, B, C, or D). For example, during 400 consecutive training trials, the visual signal might appear successively in locations DBCACBDCA until the subjects have been through this sequence 40 times. With practice, subjects gradually learn a sequence of skilled finger movements in response to the changing visual signal. Skill learning is reflected in gradually improved response speed, as subjects begin to predict where the visual signal will appear. However, if the sequence is suddenly changed, performance slows down again. Paul Reber and Squire found that amnesic patients learned this task quite well, though when tested directly the patients exhibited no awareness of the sequence.

Studies using functional MRI have identified areas of the brain that are activated during motor skill learning. Daniel Willingham and his colleagues at the University of Virginia found that sequence learning was associated with activity in left prefrontal cortex, left inferior parietal cortex, and right putamen (which together with the caudate nucleus is called the neostriatum). These
regions were active regardless of whether participants became aware of the sequence or remained unaware of the sequence. Additional areas were also active when awareness developed. Thus, it appears that a system of brain structures supports unconscious sequence learning, and these structures are engaged (and the unconscious learning occurs), even when declarative, conscious knowledge is acquired about the sequence.

The area of the motor cortex that represents the fingers also changes during the learning of skilled finger movements. Avi Karni, Leslie Ungerleider, and their colleagues at the National Institute of Mental Health had subjects practice touching the thumb with each of the other fingers in a specified order. The interesting finding was that after prolonged training, during which subjects approximately doubled the speed at which they could perform the task, the area of motor cortex that was engaged by the task became larger. This expansion, which occurred within the hand area of motor cortex, persisted for many weeks, as did the ability to perform the task at increased speed. It seems likely that, within a small region of motor cortex, practice recruited the activity of additional neurons, and did so in proportion to the dexterity and speed with which subjects could execute the sequential movements.

Additional studies by Julien Doyon, Karni, and Ungerleider identified subcortical structures important for motor skill learning. In the early phase of learning, activations were observed in the cerebellum, a large structure at the back of the brain, as well as in frontal cortex (the right anterior cingulate and dorsal premotor cortex) and in the inferior parietal cortex. Yet after a few sessions, by which time participants had achieved a high level of performance, the cerebellum and the cortical regions had substantially reduced their activity. Now activity was observed in the right neostriatum and in different cortical regions, including the supplementary motor area. Like other examples of nondeclarative memory that we have considered, including the simpler case of *Aplysia*, motor skill learning probably occurs as changes within the circuits already dedicated to performing the skill in question. One possibility is that memory storage occurs within the areas of motor cortex that are engaged during practice. An alternative possibility is that the essential synaptic changes occur in the connections from the cortex to the neostriatum.

Doyon and his colleagues found that during learning there is a shift in which brain systems are important. We have all had the experience of
carrying out a well-practiced skill, such as driving a car, in a highly automatic way. While driving along a familiar route, we might suddenly notice that we have been proceeding quite satisfactorily for several minutes, on automatic pilot as it were, and without paying conscious attention. This experience suggests that areas of the brain involved in attention and awareness may be needed early in skill learning and that these areas become less important as learning proceeds.

Early in learning, the frontal cortex tends to be engaged, consistent with its known role in storing information for temporary use. Early learning also engages the parietal cortex, an area known to be important for visual attention. Lastly, the cerebellum also tends to be active during the early stages of motor skill learning. The cerebellum is probably necessary for coordinating the specific repertoire of movements that are needed for well-executed, skilled movements and for organizing the timing of these movements. So, it appears that the frontal cortex, the parietal cortex, and the cerebellum are all engaged early in motor skill learning. Their combined activity ensures that the correct movements are assembled together and that both attention and working memory are dedicated to the task. After practice with the skill, the frontal cortex, parietal cortex, and cerebellum all show less activity, and other structures, including motor cortex, the nearby supplementary motor cortex, and the neostriatum become more engaged. These may be structures that together with the neostriatum store the skill-based information in long-term memory and allow the smooth execution of skilled movements.

An interesting feature of motor skill learning is that performance improves after a night’s sleep but not after an equivalent period of remaining awake. Matthew Walker and his colleagues at Harvard University used a sequential finger tapping task in which volunteers pressed four keys with the fingers of one hand, repeating the sequence 4-1-3-2-4 as quickly and accurately as possible. Performance speed improved by only 3.9 percent across 12 hours of waking, but improved by 20.5 percent across 12 hours of sleep. The improvement correlated best with the amount of stage 2 (nondreaming) slow-wave sleep, particularly late in the night. Similar findings have been obtained for other motor skill and perceptual skill tasks, though improved performance in these cases has sometimes been related more broadly to slow-wave sleep or to a combination of slow-wave sleep and dreaming (REM) sleep (called REM because of the characteristic rapid eye movements). What aspects of the biology of sleep are responsible for these effects are not currently understood.

Habit Learning

To learn a motor skill is to acquire a procedure for operating in the world. The same is true when we learn new habits. As we grow up, we learn to say “please” and “thank you,” to wash our hands before meals, and to take on a number of other behaviors, or habits, that are the result of training. We acquire many of these habits early in life, without obvious effort and without taking any special notice that learning is taking place. In this sense, much of habit learning is nondeclarative.

It turns out that the neostriatum is as important for habit learning as it is for the learning of motor skills. In an important study, Mark Packard, Richard Hirsch, and Norman White at McGill University trained rats to perform two different tasks that revealed key differences between habit memory and declarative memory. In one task, animals had to forage for food in the eight arms of a radial maze. On each of several days, animals were placed in the
An eight-arm radial maze used to compare declarative memory and habit memory in the rat. In the task of declarative memory, food is available at the end of each arm (lower left). With practice, a normal rat will learn to find all the food by entering each arm just once, following a path like that indicated. In the task of habit memory (lower right), food is available in only four arms, which are illuminated, and the rat learns to visit these arms.

A task that used the same apparatus, animals had to learn to visit the four arms (out of eight) that were signaled by a light. Now, only these four lit arms contained a food reward. After about two weeks of training, animals gradually learned to enter the correct arms. In this case, learning was disrupted by damage to the caudate nucleus but not by damage to the hippocampal system. This dissociation between the effects of hippocampal and caudate damage results from the fact that these two tasks, though similar at first glance, are fundamentally different. In performing the foraging task, an animal acquires and uses information about single events; that is, it must remember the specific location it has just visited on a given day. What needs to be remembered is unique to each session and changes from day to day. This type of learning requires the hippocampus. In contrast, the other task is constant from day to day, and the animal must learn about its regularities. Some arms always contain a food reward, and the rat gradually acquires this information through repetition. This second task is an example of habit learning.

It has been difficult to study habit learning in human beings because we tend to memorize each step of a task whenever we can and will engage a declarative memory strategy for tasks that rats or even monkeys learn nondeclaratively as a habit. For example, we could learn which four arms of a maze (out of eight) are the correct ones in just a few trials by quickly memorizing the location of the correct arms. There is no need to build up a habit, because we have available a very efficient declarative memory system, specialized for rapid learning. By contrast, rats can learn only gradually to discriminate the rewarded maze arms from the unrewarded arms. Perhaps rats learn to discriminate maze arms the way humans would learn to discriminate fine wines from mediocre wines or original paintings.
from forgeries. In these cases, learning proceeds gradually as one learns the relevant dimensions of the problem. Thus, rats learn gradually, without depending on the hippocampus, because they are not memorizing the task but slowly mastering the problem, as we would a skill.

Scientists can study habit learning in humans if they take special steps to design a task that resists memorization. Barbara Knowlton and Squire used a task developed by Mark Gluck at Rutgers University. The task is presented as a game of predicting the weather. On each trial the subject tries to predict from cards that are presented whether the outcome will be rain or sunshine. Four different cards are used, and on each trial one, two, or three of them can appear. Each card is independently and probabilistically related to the outcome, and the two outcomes occur equally often. For example, one of the four cards is associated with sunshine 75 percent of the time and with rain 25 percent of the time. Another card predicts sunshine 57 percent of the time and rain 43 percent of the time. Each card has its own predictive relationship to the outcome. On each trial, a subject makes a choice of rain or sunshine and immediately receives feedback signaling whether the choice was correct or incorrect. Because of the probabilistic nature of the task, it is impossible to choose correctly all the time. Accordingly, subjects have little success trying to memorize a right answer to each set of cues, and they end up making guesses based on a kind of gut feeling. Most subjects report that they have little sense that they are learning anything at all. Nevertheless, normal subjects do learn about what the cards signify, and they gradually improve their ability to predict the correct outcome of the weather. Amnesic patients learn at the same rate as normal subjects. During 50 training trials, both groups improve from an initial score of 50 percent correct (corresponding to chance performance) to about 65 percent correct. Despite their normal performance on the prediction task, the amnesic patients are markedly impaired at answering explicit factual questions about the training episode.

Patients with diseases that affect the caudate nucleus, such as Huntington’s disease or Parkinson’s disease, are unable to learn this same weather-prediction task. During 50 training trials, these patients chose correctly no better than 53 percent of the time in any 10-trial block. Thus, the caudate nucleus is important for some kinds of habit learning in humans, just as it is in experimental animals.

Russell Poldrack and his colleague at UCLA used functional magnetic resonance imaging (fMRI) to illustrate the importance of the caudate nucleus during learning of the weather-prediction task. Volunteers learned either the weather-prediction task or a similar task where they memorized a weather outcome for each of several card combinations. The caudate nucleus
Memory for Skills, Habits, and Conditioning

In these horizontal MRI images of the human brain, yellow areas indicate where activation increased more during learning of the weather-prediction task than during learning of a similar task that encouraged memorization. Conversely, blue areas indicate where activation increased more during the memorization task than during the weather-prediction task. The yellow arrow indicates the caudate nucleus. The white arrow indicates the medial temporal lobe.

was more active during the weather-prediction task than during the memorization task. Activity in the medial temporal lobe exhibited the opposite pattern. Furthermore, across subjects, activity in the medial temporal lobe and the caudate nucleus was negatively correlated, consistent with the idea that subjects brought either a declarative or a nondeclarative strategy to learning. Additional experiments showed that, when subjects learned the weather-prediction task, the medial temporal lobe was initially active and the caudate region was inactive. The medial temporal lobe then quickly became inactive, and the caudate region became active for the remainder of learning. These findings suggest that subjects initially try to memorize the task structure and then engage a nondeclarative memory strategy that permits gradual acquisition of the task.

The fact that humans can accomplish habit learning with the support of the caudate nucleus raises the possibility that habit learning might be able to substitute for declarative memory when declarative memory is impaired. If so, does the learning occur unconsciously, in the absence of awareness for what has been learned? To what extent can one memory system substitute for another?

This question can be studied with concurrent discrimination learning, a standard task that has been used to study mammalian memory for more than 50 years. Typically, eight pairs of objects are presented five times each day, one pair at a time in mixed order for a total of 40 trials. One object in each pair is always correct, and a choice of the correct object is rewarded. Humans readily learn this task in one or two days. This task ordinarily depends on declarative memory, as indicated by the fact that the subjects who perform well can describe

The eight-pair concurrent discrimination task. Each pair of objects is presented one at a time, with one of the objects consistently designated as “correct.” Subjects try to learn which object is correct in each pair by trial and error. Typically, 40 trials are given per session. On each trial, subjects choose one of the objects and are given feedback as to whether the choice is correct. The spatial position of the correct object varies from trial to trial.
the objects and have other conscious knowledge about what they have done. Furthermore, amnesic patients who are deficient at declarative memory exhibit little learning during the period that their healthy counterparts master the task.

Peter Bayley, Jennifer Frascino, and Squire tested the ability of two severely amnesic patients (E.P. and G.P.) to learn the concurrent discrimination task. Both patients have large medial temporal lobe lesions as the result of herpes simplex encephalitis. Despite their profoundly impaired declarative memory, E.P. and G.P. learned gradually during 36 and 28 sessions, respectively. Their successful learning was not accompanied by reportable knowledge about the nature of the task. For example, at the beginning of the training sessions, they could not describe the task, the instructions, or the objects.

To test whether the acquired knowledge was rigidly organized, as is thought to occur for habit learning, both patients attempted a sorting task at the conclusion of formal training. All 16 objects were placed together in the center of a table, and the patients were asked to sort the objects into two piles according to whether an object had been designated as correct or incorrect in the just-learned discrimination task. This sorting task was straightforward for the control group, but the two amnesic patients, E.P. and G.P., failed it altogether. Indeed, their scores on two different attempts were no better than could have been achieved by guessing.

These findings show that humans have a robust capacity for habit learning that can operate even when a task invites subjects to use declarative memory and memorize the correct and incorrect objects. What is learned in this circumstance is quite different from what can be learned declaratively. The information is inflexible, outside of awareness, and is not expressed as knowledge as one ordinarily uses the term. What is learned is expressed in performance, as a set of responses that may or may not be correct.

Reward-based learning of this kind can be analyzed at the cellular level. Wolfram Schultz and his colleagues at the University of Cambridge in England have recorded neuronal responses from awake monkeys in two regions of the midbrain (the substantia nigra and the ventral tegmental area), where a high percentage of the neurons use dopamine as a neurotransmitter. The substantia nigra provides a major input to the caudate nucleus, and both the substantia nigra and the caudate are affected in Parkinson’s disease.

Schultz trained monkeys to expect a juice reward 1.5 seconds after the presentation of a visual pattern. Learning was evident when the monkeys began to lick at a spout in anticipation of the reward. At the beginning of training, the majority of dopamine neurons fired whenever the reward was given. Later, after the monkeys were performing the task well, these same neurons
Healthy volunteers easily mastered the eight-pair concurrent discrimination task within three sessions (left panel). Three to six days later they exhibited flexible knowledge of what they had learned by successfully sorting all 16 objects according to whether the object had been designated as correct or incorrect (gray bar). Patient E.P. gradually learned the object pairs across 18 weeks and 36 sessions (middle panel). Five days later, and then again after 17 days, he failed the sorting task (dark blue bar), but performed perfectly when the object-pair task was presented in its original format (light blue bar). Patient G.P. learned gradually during 14 weeks and 28 sessions (right panel). Like E.P., he failed the sorting task on two different occasions (dark blue bar), but performed well when the original task format was reinstated (light blue bar). The dashed line indicates the performance score that could be achieved by guessing.

fired in response to the visual cue, which reliably predicted the reward, but the neurons did not fire in response to the reward itself. Thus, dopamine neurons can signal that a reward is coming. Importantly, the neuronal response to the reward itself reflects the discrepancy between the reward and how well it is predicted (a prediction error). An unpredicted reward (as would occur at the beginning of training) elicits a strong response from dopamine neurons. In contrast, a fully predicted reward elicits no response. The strength of the response also covaries with the value of the reward. Rewards that fail to produce dopamine signals fail to support learning.

The ability to predict reward is central to the learning process, and dopamine neurons provide an internal mechanism for reward-driven and feedback-guided learning. The caudate and putamen receive overlapping inputs from both sensory cortex and motor cortex, and this double set of inputs (in conjunction with a reward signal from the midbrain) could form a basis for associating stimuli and responses and for influencing behavioral choices. These same reward signals are also distributed to widespread target structures, including higher areas of the brain like frontal cortex that are important for attention and the organization of action. In this way, behavioral choices constructed in the striatum could be modulated by attention and other factors relevant to decision making in the real world.

**Perceptual and Cognitive Skills**

Skill learning is largely concerned with motor skills: how we learn coordinated movements of the hands and feet to meet particular purposes. However, there are also examples of skillful behavior that are not based on learned movements but
that nevertheless involve acquiring skillful ways of interacting with the world. When we learn to read our native language, for example, we initially move haltingly from word to word, but after practice we read quickly, moving the eyes to a new location about four times a second and taking the meaning from more than 300 words in one minute. Similarly, when we learn to program a computer, we first compose and record one command at a time, but eventually we move through mental operations faster than we can type them on the keyboard. These skills are the result of gradual improvement in the perceptual and cognitive procedures that we all use when we perceive, think, and solve problems.

The first example of nonmotor skill learning found to be independent of the medial temporal lobe was a reading skill. As we mentioned in Chapter 8, Neal Cohen and Squire showed in 1980 that amnesic patients learned the skill of reading mirror-reversed words at a fully normal rate and retained the skill at a normal level three months later. They were able to learn normally despite the fact that some of the patients did not remember the learning sessions and on formal tests failed to recognize the words they had read.

Skill learning also occurs when we read ordinary text. Gail Musen and Squire exploited the fact that when individuals read aloud repeatedly the same passage of connected prose, the time they require to move through the passage decreases a little with each reading (up to some limit, of course). Thus, with successive readings, the typeface, the letters and words, even the ideas expressed in the text, become easier to perceive. As a result, the material is processed more quickly. However, this improvement in reading speed does not depend on remembering the text in any ordinary sense. Amnesic patients exhibit the same improvement in reading speed as normal subjects, despite the fact that the patients do poorly on memory tests that ask about the content of the passage.

Other examples of skill-based learning have even more of a cognitive flavor than reading skills do. Diane Berry and Donald Broadbent at the University of Cambridge in England used a task that subjects tried to solve on a computer. The subjects imagined that they were running a sugar production factory and had to decide on each trial how many workers should be hired. The objective was to achieve a particular level of sugar production (9000 tons). The number of workers hired could vary in 12 discrete steps from 100 to 1200, and sugar production could similarly vary from 1000 to 12,000 tons.

At the outset, the computer displayed a starting level of 600 workers and announced that these workers had produced 6000 tons of sugar.
Subjects then proceeded to work at the task for 90 trials, deciding on each trial how many workers to hire in order to produce 9000 tons of sugar. The subjects were not told that sugar production was actually determined on each trial by a formula that included the number of workers hired, the previous day’s sugar production, and a small random factor.

Squire and Mary Frambah found that amnesic patients improved their performance on this task just as normal subjects did. Both groups gradually homed in on the correct strategy. All subjects learned not to change the number of workers too abruptly, as this caused sugar production to undershoot or overshoot the target value.

In learning the sugar production task, an individual learns a cognitive skill, which at least in its early stages involves developing a feel for how to do the task. The individual does not actually memorize facts about the task but rather develops a general sense or intuition about how to proceed. This process is nondeclarative. Learning is not accompanied by awareness about how to solve the problem, and learning does not require the brain system that supports declarative memory. Much of what we call “intuition” is probably learned and is based on nondeclarative memory.

Classical Conditioning of Motor Responses and Nondeclarative Memory

As we described in Chapter 3, classical or Pavlovian conditioning is the most basic and simplest form of associative learning. It occurs when a neutral stimulus precedes and comes to predict a biologically significant stimulus such as food or shock. After many pairings of the two stimuli, the neutral stimulus reliably elicits the response that is ordinarily made to the second, biologically significant stimulus. In this way, animals learn about the causal structure of their environment, so that their future behavior is better adapted to the circumstances in which they live. The fundamental importance of classical conditioning is indicated by its wide distribution in the animal kingdom. It
has been well documented in animals as diverse as invertebrates such as *Drosophila* and *Aplysia*, lower vertebrates such as fish, and mammals such as rabbits, rodents, and dogs, and it has been explored extensively in humans as well.

One of the interesting features of classical conditioning is that it can take several forms. The standard procedure for classical conditioning, delay conditioning, is illustrated in the figure on this page. In this type of conditioning, the conditioned stimulus is presented first, and it continues to be present while the unconditioned stimulus is presented shortly thereafter. Delay conditioning is relatively reflexive and automatic and is a quintessential example of nondeclarative memory. It is intact both in amnesic patients and in experimental animals with hippocampal lesions. Indeed, work in rabbits showed that the entire forebrain can be removed and delay conditioning still occurs. However, as we shall see, a seemingly minor variation in the training procedure can create a form of classical conditioning, called trace conditioning, that requires the hippocampus, involves awareness, and has other properties of declarative memory.

This story begins with an analysis of a simple form of delay conditioning: the eyeblink response of rabbits. Typically, to condition the eyeblink response, the investigator presents a neutral conditioned stimulus (CS; usually a tone) together with an unconditioned stimulus (US; usually an airpuff to the eye) that causes the rabbit to blink. In delay conditioning, the CS is presented just prior to the US. While the CS remains on, the US is presented and the two stimuli terminate together. The temporal relationship between the CS and the US is critical. For defensive conditioning such as the eyeblink response to occur, the CS must precede the US by a fraction of a second. The optimal CS-US interval for the rabbit is 200 to 400 milliseconds. It is similar in *Aplysia* (about 500 milliseconds) and longer in humans. If the interval is longer than about a second, or if the CS occurs at the same time as the US, or if the CS occurs after the US, then conditioning does not take place. Because in classical conditioning two stimuli must be associated, it follows that the conditioning process must occur at brain sites where information about the CS and the US converge. In Chapter 3, we saw that in *Aplysia* the CS and US pathways converge on the sensory neurons of the gill withdrawal circuit.

Work by Richard Thompson and his colleagues at the University of Southern California suggests that the memory trace for classical eyeblink con-
A stereodiagram of the cerebellar cortex. The climbing fibers synapse directly on the Purkinje neurons. The mossy fibers synapse on granule cells (blue) that send out parallel fibers (the blue horizontal lines and the dots at left), which also synapse on Purkinje neurons.

Conditioning in the vertebrate is formed and stored in the cerebellum (specifically in the cerebellar cortex and in the interpositus nucleus, a small group of nerve cells lying deep in the cerebellum below the cerebellar cortex). Its unusual anatomy and connectivity help us understand how classical conditioning occurs. The cerebellum receives two major kinds of inputs, both originating in the brain stem at the base of the brain. These are the mossy fibers and the climbing fibers. The mossy fiber input arises mainly from the pons, on the frontward aspect of the brain stem, and from other brain stem sites, and travels to the granule cells of the cerebellum. The axons of the granule cells, which are within the cerebellum, constitute the so-called parallel fibers and they contact the dendrites of the Purkinje cells, also in the cerebellum. The climbing fiber input arises from a cluster of nerve cells in the brain stem called the dorsal accessory olivary nucleus. The axons of these cells synapse directly on the Purkinje cells. Thus, the two inputs to the cerebellum eventually converge on the Purkinje neurons. Each Purkinje cell receives input from many different parallel fibers and from only one climbing fiber. The Purkinje neurons themselves are important because they are the sole source of output from the cerebellar cortex. They exit the cerebellar cortex to synapse on nuclei deep in the cerebellum, including the interpositus nucleus. It is this orderly and well-understood circuitry that
A simplified schematic of the essential brain circuitry involved in eyeblink conditioning. The tone CS enters the circuitry by activating auditory neurons. The airpuff US enters the circuitry by activating neurons in the trigeminal nucleus, which receives tactile information from the skin of the face. The arrows indicate excitatory connections, and the T-junctions indicate inhibitory connections.

has made it possible to prove that the cerebellum is not just important for classical conditioning, but is also the site where the memory trace is formed and stored.

Working with the rabbit, Thompson and his colleagues first found that small lesions of the interpositus nucleus, involving about 1 cubic millimeter of tissue, completely and permanently prevent a rabbit from learning the eyeblink conditioned response (CR). The same lesion also completely and permanently abolishes retention of a CR that had already been established. In both cases, the unconditioned eyeblink that occurs in response to the airpuff is unaffected. This finding shows that the lesion has not affected the ability to perform an eyeblink, only the ability to learn an eyeblink response to a CS.

The importance of the cerebellum is indicated more directly by the fact that electrical stimulation of the two major inputs to the cerebellum can substitute for the tone CS and the airpuff US. Specifically, climbing fibers can be stimulated to evoke an eyeblink, and this electrical stimulation can then serve as a US for eyeblink conditioning. Similarly, stimulation of the mossy fibers can serve as a CS. When climbing fiber and mossy fiber stimulation are paired, behavioral conditioning occurs. That is, mossy fiber stimulation itself comes to evoke an eyeblink.

In subsequent experiments, Thompson, David Lavond, and colleagues explored the role of the cerebellum in storing the memory trace for eyeblink conditioning. They inactivated the interpositus nucleus and the overlying cerebellar cortex by cooling the tissue. Rabbits that had undergone this treatment could not learn the eyeblink CR. After the cooling had worn off, the rabbits learned the CR at the same rate as naive animals. This
result shows that the memory trace for the tone-airpuff association is stored in the cerebellum or in downstream structures. The cerebellum is not simply needed to express what has been learned by structures earlier in the flow of information. If that were the case, the CR would have been expressed as soon as the cooling wore off.

In related experiments, the output pathway from the interpositus nucleus (the superior cerebellar peduncle) was inactivated during training by injecting a drug, or one of its main brain stem targets (the red nucleus) was inactivated. In these experiments, a different effect was observed. In this case, the conditioned eyerink response did not appear during training because motor performance was blocked. However, when the inactivation wore off, the CR was fully evident from the beginning of the test session. This result means that the learning must have occurred upstream from the red nucleus. Memory traces must have been formed during the inactivation, and these memory traces could then be expressed in performance when the inactivation was removed. This body of work provides strong evidence that the essential memory trace for eyerink conditioning is formed and stored in a small region of the cerebellum. Studies of eyerink conditioning provide the most complete information currently available about where a memory is located in the vertebrate brain.

Purkinje cells are inhibitory: when they fire, they produce an inhibitory action on cerebellar deep nuclei, including neurons in the interpositus nucleus. Purkinje cells thus act to decrease the firing of interpositus neurons. Yet, if conditioning is to increase the frequency of eyerinks to the conditioned stimulus, one should expect it to result in the increased firing of interpositus neurons. This logic implies that Purkinje neurons must decrease their firing during conditioning. In 1982, Masao Ito, then at the University of Tokyo, discovered how this might occur when he discovered the phenomenon of long-term depression (LTD).

LTD is a promising candidate for the synaptic mechanism underlying eyerink conditioning. LTD occurs when parallel fiber and climbing fiber inputs to the cerebellum are activated in close temporal proximity and at low frequencies (1 to 4 hertz). The result is a decrease in the strength of the parallel fiber synapses onto Purkinje neurons. In simplified preparations, LTD lasts for the duration of the experiment, up to several hours. LTD appears to be mediated entirely postsynaptically—that is, by the Purkinje cell itself. The climbing fiber serves simply to depolarize the Purkinje cell, which allows influx of Ca$^{2+}$. Roger Tsien and his colleagues at the University of California, San Diego, showed that the parallel fiber stimulation contributes to LTD by generating the gaseous messenger nitric oxide, which then acts to elevate cyclic guanosine monophosphate (cGMP) in the Purkinje cell. cGMP in turn activates a protein kinase (PKG). The result is that Purkinje cells become less responsive to input, presumably due to a reduced sensitivity of their non-NMDA glutamate receptors. When they become less sensitive to input, they decrease their firing and reduce their inhibitory control over interpositus neurons.

The cerebellum is not simply a structure for allowing eyerink conditioning to occur. Rather, eyerink conditioning is one example of a discrete motor response, and the classical conditioning of all discrete motor responses is thought to require the cerebellum. In addition, the cerebellum is important for the learning and performance of motor tasks that require the coordination of complex movements. Thus, the cerebellum has a critical role in much of motor learning. Richard Ivry at the University of California, Berkeley, has proposed more broadly that the cerebellum makes a specific contribution to timing, which is important
for both motor control and perception. He found that patients with cerebellar lesions failed tasks in which they must judge the temporal interval between pairs of tones. The deficit is not perceptual in itself because the patients had no difficulty judging the relative loudness of two tones. Rather, the cerebellum appears to have a role in timing that includes both the timing of perceptual events and the timing of motor actions. Ito has suggested that the importance of the cerebellum in coordinating motor response may also extend to the coordination of thought itself. In this context, eyeblink conditioning is simply the best-understood example in vertebrates of a learned behavior that requires precise timing, the formation of an association between two events, and the gradual development of coordinated behavior.

Classical Conditioning and Declarative Memory

The analysis of delay eyeblink conditioning has revealed a very basic and relatively simple form of learning. However, classical conditioning also includes more complex kinds of learning that turn out to have characteristics of declarative memory. Consider the case of trace conditioning. This type of conditioning is a variant of classical conditioning in which a short interval (lasting from 500 to 1000 milliseconds) is interposed between the offset of the CS and the onset of the US. Its name comes from the fact that the CS must leave some trace in the nervous system in order for a CS-US association to be established. This small variation creates an entirely new situation, as can be seen from the fact that animals with hippocampal lesions fail to acquire the conditioning. The question is what aspect of trace conditioning requires the hippocampus and why trace conditioning might in fact involve declarative memory.

To address this question, Robert Clark and Squire tested amnesic patients and normal volunteers on two versions of delay conditioning and two versions of trace conditioning, and then assessed the extent to which subjects became aware of the temporal relationships between the CS and the US. Amnesic patients acquired delay conditioning at a normal rate but failed to acquire trace conditioning. The normal volunteers acquired delay conditioning whether or not they were aware of the CS-US relationship, but awareness was a prerequisite for successful trace conditioning. In further experiments, trace conditioning occurred reliably when subjects were told before training about how the CS and US would be related. Conversely, trace conditioning did not occur when subjects could not develop an awareness of the CS-US relationship, because they had to perform an attention-demanding secondary task concurrently with the conditioning trials.

Thus, like other tasks of declarative memory that are impaired after hippocampal lesions, trace conditioning requires individuals to acquire and retain conscious knowledge across a considerable time span (in this case, the 20- to 30-minute conditioning session). A likely reason that trace conditioning requires declarative knowledge is that the trace interval between the CS and the US makes it difficult to process the CS-US relationship in an automatic, reflexive way. Rather, the situation is probably so complex that the stimuli and their temporal relationship to each other must be represented in the cortex. As discussed in Chapter 5, the hippocampus and related structures then would work jointly with the cortex to establish a usable representation that can persist as memory. People may develop awareness about
Performance during classical conditioning of the eyeblink response by amnesic patients and four groups of normal volunteers. Each 20-trial block included 10 CS+ trials in which a tone (or white noise) occurred together with an airpuff to the eye (the US) and 10 CS− trials in which a tone (or white noise) occurred but the US did not. The data are presented as percent differential conditioned eyeblink responses for each block of 20 trials—that is, percent conditioned responses to the positive conditioned stimulus (CS+) minus percent conditioned responses to the negative conditioned stimulus (CS−). Only groups that passed a true/false test about the relationship among the CS+, the CS−, and the US, and were thus considered aware, acquired trace conditioning (bottom graphs). All the groups, whether aware or not, acquired delay conditioning (top graphs).
a task whenever the hippocampus and cortex are engaged during learning. By analogy, those learning and memory tasks that are failed by animals with hippocampal lesions may be tasks for which intact animals must acquire some awareness.

Trace conditioning differs from delay conditioning in its dependence on the hippocampus. However, trace conditioning resembles delay conditioning in that it also depends on the cerebellum. In trace conditioning, just as in delay conditioning, a nondeclarative learning circuit in the cerebellum is required for the generation of a well-timed conditioned response. One possibility is that a representation of the CS–US relationship develops in the cortex, and CS and US information then becomes available to the cerebellum in a format that the cerebellum can use.

Kaori Takehara and her colleagues at the University of Tokyo clarified the relationship between the hippocampus, cerebellum, and cortex in trace eyeblink conditioning. Rats were given bilateral lesions of the dorsal hippocampus, medial prefrontal cortex, or cerebellum at one day, one week, two weeks, or four weeks after the animals acquired the conditioned response (CR). The hippocampal lesion disrupted a recently acquired CR but not a remotely acquired CR. The cerebellar lesion disrupted both a recently and remotely acquired CR. The medial prefrontal lesion had a mild, albeit significant, effect on a recently acquired CR and produced a progressively more severe impairment as the learning-lesion interval increased.

These findings indicate that the cerebellum is always necessary for production of the CR and that there is reorganization in the role of other brain regions as time passes after learning. The hippocampus, and the cortex to a lesser extent, are essential shortly after learning. With time, the hippocampus becomes unnecessary, and medial prefrontal cortex becomes gradually more important. Accordingly, medial prefrontal cortex is one candidate structure where critical information about the CS–US relationship could be represented and elaborated over time. Alternatively, the medial prefrontal cortex may be important for retrieval of a memory stored elsewhere. It is usually more difficult to retrieve a remote memory than a recent one, and this could explain the particularly severe impairment produced by the cortical lesion four weeks after learning.

 Chapters 8 and 9 have illustrated the broad range of nondeclarative forms of learning and memory, and have shown how the different forms depend on different brain systems. Priming and perceptual learning are intrinsic to the perceptual machinery of the cortex. Emotional memory requires the amygdala. Skill and habit learning depend crucially on the neostriatum. Classical conditioning of motor responses requires the cerebellum. As we saw in Chapters 2 and 3, many forms of nondeclarative memory are also well developed in invertebrate animals. These forms of learning, such as habituation, sensitization, and classical conditioning, have been preserved through evolutionary history, and they are present in all animals with a sufficiently developed nervous system, from invertebrates such as Aplysia and Drosophila to vertebrates, including humans. Vertebrates, of course, have evolved more complex forms of skill learning and habit learning than invertebrates, corresponding to their more complex perceptual and motor repertoires.

These various forms of nondeclarative memory do not require the participation of the medial temporal lobe memory system. They are ancient in evolutionary terms, they are reliable
and consistent, and they provide for myriad unconscious ways of responding to the world. In no small part, by virtue of the unconscious status of these forms of memory, they create much of the mystery of human experience. Here arise the dispositions, habits, and preferences that are inaccessible to conscious recollection, but that nevertheless are shaped by past events, influence our behavior and mental life, and are an important part of who we are.