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Patient H. M. has a relatively pure amnesia.

His intellectual ability and his immediate verbal

memory appear to be normal. He can repeat seven numbers

forward and five numbers backward, and he can carry on

conversations, rephrase sentences, and perform mental

arithmetic. He is unable to remember events that occurred

during several years preceding his brain surgery, but he can

recall older memories very well. He showed no personality

change after the operation, and he appears to be generally

polite and good-natured.

However, since the operation, H. M. has been unable to

learn anything new. He cannot identify by name people he

has met since the operation (performed in 1953, when he

was twenty-seven years old). His family moved to a new

house after his operation, and he never learned how to get

around in the new neighborhood. (He now lives in a nursing

home, where he can be cared for.) He is aware of his disorder

and often says something like this:

Every day is alone in itself, whatever enjoyment I’ve

had, and whatever sorrow I’ve had. . . . Right now,

I’m wondering. Have I done or said anything amiss?

You see, at this moment everything looks clear to

me, but what happened just before? That’s what

worries me. It’s like waking from a dream; I just

don’t remember. (Milner, 1970, p. 37)

H. M. is capable of remembering a small amount of verbal

information as long as he is not distracted; constant rehearsal

can keep information in his immediate memory for a long

time. However, rehearsal does not appear to have any longterm

effects. If he is distracted for a moment, he will completely

forget whatever he had been rehearsing. He works very well at

repetitive tasks. Indeed, because he so quickly forgets what previously

happened, he does not easily become bored. He can

endlessly reread the same magazine or laugh at the same jokes,

finding them fresh and new each time. His time is typically

spent solving crossword puzzles and watching television.

Experiences change us; encounters with our environment

alter our behavior by modifying our

nervous system. As many investigators have said,

an understanding of the physiology of memory

is the ultimate challenge to neuroscience research. The

brain is complex, and so are learning and remembering.

However, despite the difficulties, the long years of work

finally seem to be paying off. New approaches and new

methods have evolved from old ones, and real progress

has been made in understanding the anatomy and physiology

of learning and remembering.

THE NATURE OF LEARNING

*Learning* refers to the process by which experiences

change our nervous system and hence our behavior. We

refer to these changes as *memories.* Although it is convenient

to describe memories as if they were notes placed in

filing cabinets, this is certainly not the way experiences are

reflected within the brain. Experiences are not “stored”;

rather, they change the way we perceive, perform, think,

and plan. They do so by physically changing the structure

of the nervous system, altering neural circuits that participate

in perceiving, performing, thinking, and planning.

Learning can take at least four basic forms: perceptual

learning, stimulus-response learning, motor learning,

and relational learning. **Perceptual learning** is the

ability to learn to recognize stimuli that have been perceived

before. The primary function of this type of

learning is the ability to identify and categorize objects

(including other members of our own species) and situations.

Unless we have learned to recognize something,

we cannot learn how we should behave with respect to

it—we will not profit from our experiences with it, and

profiting from experience is what learning is all about.

Each of our sensory systems is capable of perceptual

learning. We can learn to recognize objects by their

visual appearance, the sounds they make, how they feel,

or how they smell. We can recognize people by the

shape of their faces, the movements they make when

they walk, or the sound of their voices. When we hear

people talk, we can recognize the words they are saying

and, perhaps, their emotional state. As we shall see, perceptual

learning appears to be accomplished primarily

by changes in the sensory association cortex. That is,

learning to recognize complex visual stimuli involves

changes in the visual association cortex, learning to recognize

complex auditory stimuli involves changes in the

auditory association cortex, and so on.

**Stimulus-response learning** is the ability to learn to

perform a particular behavior when a particular stimulus

is present. Thus, it involves the establishment of connections

between circuits involved in perception and

those involved in movement. The behavior could be an

automatic response such as a defensive reflex, or it

could be a complicated sequence of movements.

Stimulus-response learning includes two major categories

of learning that psychologists have studied extensively:

*classical conditioning* and *instrumental conditioning*.

**perceptual learning** Learning to recognize a particular stimulus.

**stimulus-response learning** Learning to automatically make a

particular response in the presence of a particular stimulus; includes

classical and instrumental conditioning.

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**FIGURE 13.1** ■ **A Simple Neural Model of .**

**Classical Conditioning .**

When the 1000-Hz tone is presented just before the puff of

air to the eye, synapse T is strengthened.

Neuron in

auditory

system

Synapse T

(weak)

1000-Hz

tone

Puff of

air to

the eye

Neuron in

somatosensory

system

Synapse P

(strong)

Blink

**Classical conditioning** is a form of learning in which

an unimportant stimulus acquires the properties of an

important one. It involves an *association between two stimuli*.

A stimulus that previously had little effect on behavior

becomes able to evoke a reflexive, species-typical behavior.

For example, a defensive eyeblink response can be conditioned

to a tone. If we direct a brief puff of air toward a

rabbit’s eye, the eye will automatically blink. The response

is called an **unconditional response (UR)** because it occurs

unconditionally, without any special training. The stimulus

that produces it (the puff of air) is called an

**unconditional stimulus (US).** Now we begin the training.

We present a series of brief 1000-Hz tones, each followed

500 ms later by a puff of air. After several trials the rabbit’s

eye begins to close even before the puff of air occurs.

Classical conditioning has occurred; the **conditional stimulus**

**(CS**—the 1000-Hz tone) now elicits the **conditional**

**response (CR**—the eyeblink). (See ***Figure 13.1.***)

When classical conditioning takes place, what kinds

of changes occur in the brain? Figure 13.1. shows a simplified

neural circuit that could account for this type of

learning. For the sake of simplicity we will assume that the

US (the puff of air) is detected by a single neuron in the

somatosensory system and that the CS (the 1000-Hz tone)

is detected by a single neuron in the auditory system. We

will also assume that the response—the eyeblink—is controlled

by a single neuron in the motor system. Of course,

learning actually involves many thousands of neurons—

sensory neurons, interneurons, and motor neurons—but

the basic principle of synaptic change can be represented

by this simple figure. (See ***Figure 13.1.***)

Let’s us see how this circuit works. If we present a

1000-Hz tone, we find that the animal makes no reaction

because the synapse connecting the tone-sensitive neuron

with the neuron in the motor system is weak. That is,

when an action potential reaches the terminal button of

synapse T (tone), the excitatory postsynaptic potential

(EPSP) that it produces in the dendrite of the motor

neuron is too small to make that neuron fire. However,

if we present a puff of air to the eye, the eye blinks. This

reaction occurs because nature has provided the animal

with a strong synapse between the somatosensory neuron

and the motor neuron that causes a blink (synapse

P, for “puff”). To establish classical conditioning, we first

present the 1000-Hz tone and then quickly follow it with

a puff of air. After we repeat these pairs of stimuli several

times, we find that we can dispense with the air puff; the

1000-Hz tone produces the blink all by itself.

Over fifty years ago, Donald Hebb proposed a rule

that might explain how neurons are changed by experience

in a way that would cause changes in behavior

(Hebb, 1949). The **Hebb rule** says that if a synapse

repeatedly becomes active at about the same time that

the postsynaptic neuron fires, changes will take place in

the structure or chemistry of the synapse that will

strengthen it. How would the Hebb rule apply to our circuit?

If the 1000-Hz tone is presented first, then weak

synapse T (for “tone”) becomes active. If the puff is presented

immediately afterward, then strong synapse P

becomes active and makes the motor neuron fire. The

act of firing then strengthens any synapse with the motor

neuron *that has just been active.* Of course, this means

synapse T. After several pairings of the two stimuli and

after several increments of strengthening, synapse T

becomes strong enough to cause the motor neuron to

fire by itself. Learning has occurred. (See ***Figure 13.1.***)

When Hebb formulated his rule, he was unable to

determine whether it was true or false. Now, finally,

enough progress has been made in laboratory techniques

that the strength of individual synapses can be

determined, and investigators are studying the physiological

bases of learning. We will see the results of some

of these approaches in the next section of this chapter.

The second major class of stimulus-response learning

is **instrumental conditioning** (also called *operant*

**classical conditioning** A learning procedure; when a stimulus that

initially produces no particular response is followed several times by

an **unconditional stimulus (US)** that produces a defensive or

appetitive response (the **unconditional response—UR**), the first

stimulus (now called a **conditional stimulus—CS**) itself evokes the

response (now called a **conditional response—CR**).

**Hebb rule** The hypothesis proposed by Donald Hebb that the

cellular basis of learning involves strengthening of a synapse that

is repeatedly active when the postsynaptic neuron fires.

**instrumental conditioning** A learning procedure whereby the

effects of a particular behavior in a particular situation increase

(reinforce) or decrease (punish) the probability of the behavior; also

called *operant conditioning*.

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*conditioning*). Whereas classical conditioning involves

automatic, species-typical responses, instrumental conditioning

involves behaviors that have been learned.

And whereas classical conditioning involves an association

between two stimuli, instrumental conditioning

involves an *association between a response and a stimulus.*

Instrumental conditioning is a more flexible form of

learning. It permits an organism to adjust its behavior

according to the consequences of that behavior. That is,

when a behavior is followed by favorable consequences,

the behavior tends to occur more frequently; when it is

followed by unfavorable consequences, it tends to occur

less frequently. Collectively, “favorable consequences”

are referred to as **reinforcing stimuli,** and “unfavorable

consequences” are referred to as **punishing stimuli.** For

example, a response that enables a hungry organism to

find food will be reinforced, and a response that causes

pain will be punished. (Psychologists often refer to these

terms as *reinforcers* and *punishers*.)

Let’s consider the process of reinforcement. Briefly

stated, reinforcement causes changes in an animal’s nervous

system that increase the likelihood that a particular

stimulus will elicit a particular response. For example,

when a hungry rat is first put in an operant chamber (a

“Skinner box”), it is not very likely to press the lever

mounted on a wall. However, if it does press the lever and

if it receives a piece of food immediately afterward, the

likelihood of its pressing the lever increases. Put another

way, reinforcement causes the sight of the lever to serve as

the stimulus that elicits the lever-pressing response. It is

not accurate to say simply that a particular behavior

becomes more frequent. If no lever is present, a rat that

has learned to press one will not wave its paw around in

the air. The *sight of a lever* is needed to produce the

response. Thus, the process of reinforcement strengthens

a connection between neural circuits involved in perception

(the sight of the lever) and those involved in movement

(the act of lever pressing). As we will see later in this

chapter, the brain contains reinforcement mechanisms

that control this process. (See ***Figure 13.2.***)

The third major category of learning, **motor learning,**

is actually a component of stimulus-response learning.

For simplicity’s sake we can think of perceptual

learning as the establishment of changes within the sensory

systems of the brain, stimulus-response learning as

the establishment of connections between sensory systems

and motor systems, and motor learning as the

establishment of changes within motor systems. But, in

fact, motor learning cannot occur without sensory guidance

from the environment. For example, most skilled

movements involve interactions with objects: bicycles,

pinball machines, tennis racquets, knitting needles, and

so on. Even skilled movements that we make by ourselves,

such as solitary dance steps, involve feedback

from the joints, muscles, vestibular apparatus, eyes, and

contact between the feet and the floor. Motor learning

differs from other forms of learning primarily in the

degree to which new forms of behavior are learned; the

more novel the behavior, the more the neural circuits

in the motor systems of the brain must be modified.

(See ***Figure 13.3.***)

**FIGURE 13.2** ■ **A Simple Neural Model of Instrumental .**

**Conditioning .**

Reinforcing stimulus

(e.g., food)

Reinforcement

system

Stimulus

(e.g., sight

of lever)

Neural circuit that

detects a particular

stimulus

Neural circuit

that controls a

particular behavior

Behavior

(e.g., lever

press)

When rat

presses lever,

it receives food

Reinforcement system

strengthens this connection

Perceptual System Motor System

**reinforcing stimulus** An appetitive stimulus that follows a

particular behavior and thus makes the behavior become more

frequent.

**punishing stimulus** An aversive stimulus that follows a particular

behavior and thus makes the behavior become less frequent.

**motor learning** Learning to make a new response.

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A particular learning situation can involve varying

amounts of all three types of learning that I have

described so far: perceptual, stimulus-response, and

motor. For example, if we teach an animal to make a

new response whenever we present a stimulus it has

never seen before, the animal must learn to recognize

the stimulus (perceptual learning) and make the

response (motor learning), and a connection must be

established between these two new memories (stimulusresponse

learning). If we teach the animal to make a

response that it has already learned whenever we present

a new stimulus, only perceptual learning and stimulusresponse

learning will take place.

The three forms of learning I have described so far

consist primarily of changes in one sensory system,

between one sensory system and the motor system, or in

the motor system. But obviously, learning is usually

more complex than that. The fourth form of learning

involves learning the *relationships* among individual stimuli.

For example, a somewhat more complex form of

perceptual learning involves connections between different

areas of the association cortex. When we hear the

sound of a cat meowing in the dark, we can imagine

what a cat looks like and what it would feel like if we

stroked its fur. Thus, the neural circuits in the auditory

association cortex that recognize the meow are somehow

connected to the appropriate circuits in the visual

association cortex and the somatosensory association

cortex. These interconnections, too, are accomplished

as a result of learning.

Perception of spatial location—*spatial learning*—

also involves learning about the relationships among

many stimuli. For example, consider what we must learn

to become familiar with the contents of a room. First, we

must learn to recognize each of the objects. In addition,

we must learn the relative locations of the objects with

respect to each other. As a result, when we find ourselves

in a particular place in the room, our perceptions of

these objects and their locations relative to us tell us

exactly where we are.

Other types of relational learning are even more

complex. *Episodic learning*—remembering sequences of

events (episodes) that we witness—requires us to keep

track of and remember not only individual events but

also the order in which they occur. As we will see in the

last section of this chapter, a special system that involves

the hippocampus and associated structures appears to

perform coordinating functions required for many

types of learning that go beyond simple perceptual,

stimulus-response, or motor learning.

**FIGURE 13.3** ■ **An Overview of Perceptual, Stimulus-Response .**

**(S-R), and Motor Learning .**

Perceptual System Motor System

Stimulus

Changes in

neural circuit

that detects

a particular

stimulus

Changes in

neural circuit

that controls

a particular

behavior

Response

Perceptual

learning

Motor

learning

S-R learning

**InterimSummary**

**The Nature of Learning**

Learning produces changes in the way we perceive, act,

think, and feel. It does so by producing changes in the nervous

system in the circuits responsible for perception, in those

responsible for the control of movement, and in connections

between the two.

Perceptual learning consists primarily of changes in

perceptual systems that make it possible for us to recognize

stimuli so that we can respond to them appropriately.

Stimulus-response learning consists of connections between

perceptual and motor systems. The most important forms are

classical and instrumental conditioning. Classical conditioning

occurs when a neutral stimulus is followed by an unconditional

stimulus (US) that naturally elicits an unconditional

response (UR). After this pairing, the neutral stimulus becomes

a conditional stimulus (CS); it now elicits the response by itself,

which we refer to as the conditional response (CR).

Instrumental conditioning occurs when a response is

followed by a reinforcing stimulus, such as a drink of water

for a thirsty animal. The reinforcing stimulus increases the

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SYNAPTIC PLASTICITY:

LONG-TERM POTENTIATION

AND LONG-TERM DEPRESSION

On theoretical considerations alone, it would appear

that learning must involve synaptic plasticity: changes in

the structure or biochemistry of synapses that alter their

effects on postsynaptic neurons. Recent years have seen

an explosion of research on this topic, largely stimulated

by the development of methods that permit researchers

to observe structural and biochemical changes in microscopically

small structures: the presynaptic and postsynaptic

components of synapses.

Induction of Long-Term Potentiation

Electrical stimulation of circuits within the hippocampal

formation can lead to long-term synaptic changes that

seem to be among those responsible for learning. Lømo

(1966) discovered that intense electrical stimulation of

axons leading from the entorhinal cortex to the dentate

gyrus caused a long-term increase in the magnitude of

excitatory postsynaptic potentials in the postsynaptic

neurons; this increase has come to be called **long-term**

**potentiation (LTP).** (The word *potentiate* means “to

strengthen, to make more potent.”)

First, let’s review some anatomy. The **hippocampal**

**formation** is a specialized region of the limbic cortex

located in the temporal lobe. (Its location in a human

brain is shown in Figure 3.19.) Because the hippocampal

formation is folded in one dimension and then

curved in another, it has a complex, three-dimensional

shape. Therefore, it is difficult to show what it looks like

with a diagram on a two-dimensional sheet of paper.

Fortunately, the structure of the hippocampal formation

is orderly; a slice taken anywhere perpendicular to its

curving long axis contains the same set of circuits.

**Figure 13.4** shows a slice of the hippocampal formation,

illustrating a typical procedure for producing

likelihood that the other stimuli that were present when the

response was made will evoke the response. Both forms of

stimulus-response learning may occur as a result of strengthened

synaptic connections, as described by the Hebb rule.

Motor learning, although it may primarily involve

changes within neural circuits that control movement, is

guided by sensory stimuli; thus, it is actually a form of stimulusresponse

learning. Relational learning, the most complex

form of learning, includes the ability to recognize objects

through more than one sensory modality, to recognize the

relative location of objects in the environment, and to

remember the sequence in which events occurred during

particular episodes.

**Thought Question**

Can you think of specific examples of each of the categories

of learning described in this section? Can you think of some

examples that include more than one category?

long-term potentiation. The primary input to the hippocampal

formation comes from the *entorhinal cortex*.

The axons of neurons in the entorhinal cortex pass

through the *perforant path* and form synapses with the

granule cells of the *dentate gyrus.* A stimulating electrode

is placed in the perforant path, and a recording electrode

is placed in the dentate gyrus, near the granule

cells. (See ***Figure 13.4b.***) First, a single pulse of electrical

stimulation is delivered to the perforant path, and then

the resulting population EPSP is recorded in the dentate

gyrus. The **population EPSP** is an extracellular measurement

of the excitatory postsynaptic potentials (EPSP)

produced by the synapses of the perforant path axons

with the dentate granule cells. The size of the first population

EPSP indicates the strength of the synaptic connections

before long-term potentiation has taken place.

Long-term potentiation can be induced by stimulating

the axons in the perforant path with a burst of approximately

one hundred pulses of electrical stimulation,

delivered within a few seconds. Evidence that long-term

potentiation has occurred is obtained by periodically

delivering single pulses to the perforant path and

recording the response in the dentate gyrus. If the

response is greater than it was before the burst of pulses

was delivered, long-term potentiation has occurred.

(See ***Figure 13.5.***)

Long-term potentiation can be produced in other

regions of the hippocampal formation and in many

other places in the brain. It can last for several months

**long-term potentiation (LTP)** A long-term increase in the

excitability of a neuron to a particular synaptic input caused by

repeated high-frequency activity of that input.

**hippocampal formation** A forebrain structure of the temporal

lobe, constituting an important part of the limbic system; includes

the hippocampus proper (Ammon’s horn), dentate gyrus, and

subiculum.

**population EPSP** An evoked potential that represents the EPSPs

of a population of neurons.

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**FIGURE 13.5** ■ **Long-Term Potentiation .**

Population EPSPs were recorded from the dentate gyrus

before and after electrical stimulation that led to long-term

potentiation.

(From Berger, T. W. *Science,* 1984, *224,* 627–630. Copyright © 1984 by the

American Association for the Advancement of Science. Reprinted with

permission.)

Before long-term

potentiation

After long-term

potentiation

Population EPSP 1 hour 24 hours

48 hours 72 hours 96 hours

**FIGURE 13.4** ■ **The Hippocampal Formation and .**

**Long-Term Potentiation .**

The schematic shows the connections of the components of the hippocampal formation

and the procedure for producing long-term potentiation.

(Photograph from Swanson, L. W., Köhler, C., and Björklund, A., in *Handbook of Chemical Neuroanatomy. Vol. 5:*

*Integrated Systems of the CNS, Part I.* Amsterdam: Elsevier Science Publishers, 1987. Reprinted with permission.)

Schaffer

collateral

axon

Field

CA3 Field

CA1

To septum,

mammillary bodies

(a) (b)

Mossy

fiber

Dentate

gyrus

Stimulate

axons in

perforant

path

Record from

dentate gyrus

Entorhinal

cortex

Subicular

complex

Axon in

perforant

path

Schaffer

commissural

axon

Fimbria

(Bliss and Lømo, 1973). It can be produced in isolated

slices of the hippocampal formation as well as in the

brains of living animals, which allows researchers to stimulate

and record from individual neurons and to analyze

biochemical changes. The brain is removed from the

skull, the hippocampal complex is dissected, and slices

are placed in a temperature-controlled chamber filled

with liquid that resembles interstitial fluid. Under optimal

conditions a slice remains alive for up to forty hours.

Many experiments have demonstrated that longterm

potentiation in hippocampal slices can follow the

Hebb rule. That is, when weak and strong synapses to a

single neuron are stimulated at approximately the same

time, the weak synapse becomes strengthened. This

phenomenon is called **associative long-term potentiation,**

because it is produced by the association (in time)

between the activity of the two sets of synapses. (See

***Figure 13.6.***)

**associative long-term potentiation** A long-term potentiation in

which concurrent stimulation of weak and strong synapses to a

given neuron strengthens the weak ones.

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**FIGURE 13.8** ■ **Long-Term Potentiation .**

Synaptic strengthening occurs when synapses are active

while the membrane of the postsynaptic cell is depolarized.

Stimulate

axon that

forms synapse

with neuron

Dendritic

spine

Synapse is

strengthened

Pyramidal

cell

Depolarize

cell

Axon

Role of NMDA Receptors

Nonassociative long-term potentiation requires some sort

of additive effect. That is, a series of pulses delivered at a

high rate all in one burst will produce LTP, but the same

number of pulses given at a slow rate will not. (In fact, as

we shall see, low-frequency stimulation can lead to the

opposite phenomenon: long-term *depression*.) The reason

for this phenomenon is now clear. A rapid rate of stimulation

causes the excitatory postsynaptic potentials to

summate, because each successive EPSP occurs before

the previous one has dissipated. This means that rapid

stimulation depolarizes the postsynaptic membrane

much more than slow stimulation does. (See ***Figure 13.7.***)

Several experiments have shown that synaptic

strengthening occurs when molecules of the neurotransmitter

bind with postsynaptic receptors located in a

dendritic spine that is already depolarized. Kelso,

Ganong, and Brown (1986) found that if they used a

microelectrode to artificially depolarize a neuron in

field CA1 and then stimulated the axons that formed

synapses with this neuron, the synapses became

stronger. However, if the stimulation of the synapses and

the depolarization of the neuron occurred at different

times, no effect was seen; therefore, the two events had

to occur together. (See ***Figure 13.8.***)

Experiments such as the ones I just described indicate

that LTP requires two events: activation of synapses

and depolarization of the postsynaptic neuron. The

**FIGURE 13.7** ■ **The Role of Summation in .**

**Long-Term Potentiation .**

If axons are stimulated rapidly, the EPSPs produced by the

terminal buttons will summate, and the postsynaptic

membrane will depolarize enough for long-term potentiation

to occur. If axons are stimulated slowly, the EPSPs will not

summate, and long-term potentiation will not occur.

Threshold for establishment

of long-term potentiation

EPSPs produced

by a high rate of

stimulation summate

and reach the

threshold

Low rate of stimulation

does not depolarize

membrane sufficiently

Membrane potential

Stimulation Time

High Low

**FIGURE 13.6** ■ **Associative Long-Term .**

**Potentiation .**

If the weak stimulus and strong stimulus are applied at the

same time, the synapses activated by the weak stimulus will

be strengthened.

Field

CA1

Field

CA3

Dentate

gyrus

Entorhinal

cortex

Strong stimulus

Record EPSP

Weak stimulus

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explanation for this phenomenon, at least in some parts

of the brain, lies in the characteristics of a very special

type of glutamate receptor. The **NMDA receptor** has

some unusual properties. It is found in the hippocampal

formation, especially in field CA1. It gets its name from

a drug that specifically activates it: *N*-methyl-D-aspartate.

The NMDA receptor controls a calcium ion channel.

This channel is normally blocked by a magnesium ion

(Mg2+), which prevents calcium ions from entering the

cell even when the receptor is stimulated by glutamate.

But if the postsynaptic membrane is depolarized, the

Mg2+ is ejected from the ion channel, and the channel is

free to admit Ca2+ ions. Thus, calcium ions enter the cells

through the channels controlled by NMDA receptors only

when glutamate is present *and* when the postsynaptic

membrane is depolarized. This means that the ion

channel controlled by the NMDA receptor is a

neurotransmitter- *and* voltagedependent

ion channel. (See

***Figure 13.9.*** and ***MyPsychKit***

***13.1, The NMDA Receptor.***)

Cell biologists have discovered

that the calcium ion is

used by many cells as a second messenger that activates

various enzymes and triggers biochemical processes.

The entry of calcium ions through the ion channels controlled

by NMDA receptors is an essential step in longterm

potentiation (Lynch et al., 1984). **AP5** (2-amino-5-

phosphonopentanoate), a drug that blocks NMDA

receptors, prevents calcium ions from entering the dendritic

spines and thus blocks the establishment of LTP

(Brown et al., 1989). These results indicate that the activation

of NMDA receptors is necessary for the first step

in the process events that establishes LTP: the entry of

calcium ions into dendritic spines.

In Chapter 2 you learned that only axons are capable

of producing action potentials. Actually, they can

also occur in dendrites of some types of pyramidal cells,

including those in field CA1 of the hippocampal formation.

The threshold of excitation for **dendritic spikes** (as

these action potentials are called) is rather high. As far

as we know, they occur only when an action potential is

triggered in the axon of the pyramidal cell. The backwash

of depolarization across the cell body triggers a

dendritic spike, which is propagated up the trunk of the

dendrite. This means that whenever the axon of a

pyramidal cell fires, all of its dendritic spines become

depolarized for a brief time.

A study by Magee and Johnston (1997) proved that

the simultaneous occurrence of synaptic activation and

a dendritic spike strengthens the active synapse. The

investigators injected individual CA1 pyramidal cells in

hippocampal slices with calcium-green-1, a fluorescent

Animation 13.1

The NMDA Receptor

**FIGURE 13.9** ■ **The NMDA Receptor .**

The NMDA receptor is a neurotransmitter- and voltage-dependent ion channel. (a) When

the postsynaptic membrane is at the resting potential, blocks the ion channel,

preventing from entering. (b) When the membrane is depolarized, the magnesium ion

is evicted. Thus, the attachment of glutamate to the binding site causes the ion channel to

open, allowing calcium ions to enter the dendritic spine.

Ca2+

Mg2+

NMDA

Ca receptor 2+ Ca2+

Ca2+

Ca2+

Ca2+

Ca2+

Depolarization of the

membrane evicts the

magnesium ion and

unblocks the channel. Now

glutamate can open the ion

channel and permit the

entry of calcium ions.

Depolarization

Mg2+

Mg2+

(a) (b)

Molecule of

glutamate

If a molecule of glutamate

binds with the NMDA

receptor, the calcium channel

cannot open because the

magnesium ion blocks the

channel

**NMDA receptor** A specialized ionotropic glutamate receptor that

controls a calcium channel that is normally blocked by ions;

involved in long-term potentiation.

**AP5** 2-Amino-5-phosphonopentanoate, a drug that blocks

NMDA receptors.

**dendritic spike** An action potential that occurs in the dendrite of

some types of pyramidal cells.

Mg2+

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dye that permitted them to observe the influx of calcium.

They found that when individual synapses became active

at the same time that a dendritic spike had been triggered,

calcium “hot spots” occurred near the activated

synapses. Moreover, the size of the excitatory postsynaptic

potential produced by these activated synapses

became larger. In other words, these synapses became

strengthened. To confirm that the dendritic spikes were

necessary for the synaptic potentiation to take place, the

investigators infused a small amount of tetrodotoxin

(TTX) onto the base of the dendrite just before triggering

an action potential. The TTX prevented the formation

of dendritic spikes by blocking voltage-dependent

sodium channels. Under these conditions, long-term

potentiation did not occur.

I think that considering what you already know

about associative LTP, you can anticipate the role that

NMDA receptors play in this phenomenon. If weak

synapses are active by themselves, nothing happens

because the membrane of the dendritic spine does not

depolarize sufficiently for the calcium channels controlled

by the NMDA receptors to open. (Remember

that for these channels to open, the postsynaptic membrane

must first depolarize and displace the magnesium

ions that normally block them.) However, if the activity

of strong synapses located elsewhere on the postsynaptic

cell has caused the cell to fire, then a dendritic spike will

depolarize the postsynaptic membrane enough to eject

the magnesium ions from the calcium channels of the

NMDA receptors in the dendritic spines. If some weak

synapses then become active, calcium will enter the dendritic

spines and cause the synapses to become strengthened.

Thus, the special properties of NMDA receptors

account not only for the existence

of long-term potentiation

but also for its associative

nature. (See ***Figure 13.10*** and

***MyPsychKit 13.2, Associative***

***LTP.***)

Mechanisms of Synaptic Plasticity

What is responsible for the increases in synaptic

strength that occur during long-term potentiation?

Dendritic spines on CA1 pyramidal cells contain two

types of glutamate receptors: NMDA receptors and

**AMPA receptors.** Research indicates that strengthening

**FIGURE 13.10** ■ **Associative Long-Term Potentiation .**

If the activity of strong synapses is sufficient to trigger an action potential in the neuron, the

dendritic spike will depolarize the membrane of dendritic spines, priming NMDA receptors

so that any weak synapses active at that time will become strengthened.

Action potential

reaches terminal

button; glutamate

is released

Dendritic spike

washes back

along dendrite;

primes NMDA

receptors in

dendritic

spines

Dendritic

spine

Action potential

reaches terminal

button of strong

synapse; produces

strong EPSP

(depolarization)

in pyramidal cell

Strong

synapse

Dendritic

spike

Axon Action potential

in axon

Long-term

potentiation:

synapse is

strengthened

Dendrite of

pyramidal cell

Depolarization is

sufficient to trigger

action potential

in axon of

pyramidal cell

**AMPA receptor** An ionotropic glutamate receptor that controls a

sodium channel; when open, it produces EPSPs.

Animation 13.2

Associative LTP

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**FIGURE 13.11** ■ **Role of AMPA Receptors .**

**in Long-Term Potentiation .**

Two-photon laser scanning microscopy of the CA1 region of

living hippocampal slices shows delivery of AMPA receptors

into dendritic spines after long-term potentiation. The AMPA

receptors were tagged with a fluorescent dye molecule. The

two photographs at the bottom are higher magnifications

of the ones above. The arrows labeled *a* and *b* point to

dendritic spines that became filled with AMPA receptors

after the induction of long-term potentiation.

(From Shi, S.-H., Hayashi, Y., Petralia, R. S., Zaman, S. H., Wenthold, R. J.,

Svoboda, K., and Malinow, R. *Science,* 1999, *284,* 1811–1816. Copyright ©

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Before LTP After LTP

of an individual synapse appears to be accomplished by

insertion of additional AMPA receptors into the postsynaptic

membrane of the dendritic spine. AMPA

receptors control sodium channels; thus, when they are

activated by glutamate, they produce EPSPs in the

membrane of the dendritic spine. Therefore, with

more AMPA receptors present, the release of glutamate

by the terminal button causes a larger excitatory postsynaptic

potential. In other words, the synapse becomes

stronger.

Where do these new AMPA receptors come from?

Shi et al. (1999) used a harmless virus to insert a gene

for a subunit of the AMPA receptor into rat hippocampal

neurons maintained in a tissue culture. The AMPA

receptors produced by the gene had a fluorescent dye

molecule attached to them, which permitted the investigators

to use a two-photon laser scanning microscope

to see the exact location of AMPA receptors in

dendritic spines of CA1 neurons. The investigators

induced LTP by stimulating axons that form synapses

with these dendrites. Before LTP was induced, they

saw AMPA receptors clustered at the base of the dendritic

spines. Fifteen minutes after the induction of

LTP, the AMPA receptors flooded into the spines and

moved to their tips—the location of the postsynaptic

membrane. This movement of AMPA receptors did

not occur when AP5, the drug that blocks NMDA

receptors, was added to the culture medium. (See

***Figure 13.11.***)

How does the entry of calcium ions into the dendritic

spine cause AMPA receptors to move into the

postsynaptic membrane? This process appears to involve

several enzymes, including **CaM-KII** (type II calciumcalmodulin

kinase), an enzyme found in dendritic

spines. CaM-KII is a *calcium-dependent* enzyme, which is

inactive until a calcium ion binds with it and activates it.

Many studies have shown that CaM-KII plays a critical

role in long-term potentiation. For example, Silva et al.

(1992a) produced a targeted mutation against the gene

responsible for the production of CaM-KII in mice. The

mice had no obvious neuroanatomical defects, and the

responses of their NMDA receptors were normal.

However, the investigators were unable to produce LTP

in field CA1 of hippocampal slices taken from these animals.

Lledo et al. (1995) found that injection of activated

CaM-KII directly into CA1 pyramidal cells mimicked the

effects of LTP: It strengthened synaptic transmission in

those cells.

As we saw in Chapter 3, when synapses are examined

under an electron microscope, a dark band is seen

just inside the postsynaptic membrane. This band,

known as the *postsynaptic density,* contains a variety of

proteins: receptors, enzymes, messenger proteins, and

scaffolding proteins—structural proteins that anchor

the receptors, enzymes, and messengers in place

(Allison et al., 2000). Shen and Meyer (1999) used a

harmless virus to insert a gene for a fluorescent dye molecule

attached to CaM-KII into cultured hippocampal

neurons. They found that after LTP was induced, CaMKII

molecules became concentrated in the postsynaptic

densities of dendritic spines, where the postsynaptic

receptors are located. (See ***Figure 13.12.***)

Two other changes that accompany LTP are alteration

of synaptic structure and production of new

synapses. Many studies have found that the establishment

of LTP includes changes in the size and shape of

dendritic spines. For example, Bourne and Harris

(2007) suggest that LTP causes the enlargement of thin

spines into fatter, mushroom-shaped spines. Figure

13.13. shows the variety of shapes that dendritic spines

and their associated postsynaptic density can take. (See

***Figure 13.13.***) Nägerl et al. (2007) found that the establishment

of LTP caused the growth of new dendritic

spines. After about fifteen to nineteen hours, the new

spines formed synaptic connections with terminals of

nearby axons. (See ***Figure 13.14.***)

**CaM-KII** Type II calcium-calmodulin kinase, an enzyme that

must be activated by calcium; may play a role in the establishment

of long-term potentiation.

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Researchers believe that LTP may also involve

*presynaptic* changes in existing synapses, such as an

increase in the amount of glutamate that is released by

the terminal button. But how could a process that begins

postsynaptically, in the dendritic spines, cause presynaptic

changes? A possible answer comes from the discovery that

a simple molecule, nitric oxide, can communicate messages

from one cell to another. As we saw in Chapter 4,

nitric oxide is a soluble gas produced from the amino

acid arginine by the activity of an enzyme known as **nitric**

**oxide synthase.** Once produced, NO lasts only a short

time before it is destroyed. Thus, if it were produced in

dendritic spines in the hippocampal formation, it could

diffuse only as far as the nearby terminal buttons, where

it might produce changes related to the induction of LTP.

Several experiments suggest that NO may indeed be

a retrograde messenger involved in LTP. (*Retrograde*

means “moving backward”; in this context it refers to

messages sent from the dendritic spine back to the terminal

button.) Several studies have shown that drugs

that block nitric oxide synthase prevent the establishment

of LTP in field CA1 (Haley, Wilcox, and Chapman,

1992). In addition, Endoh, Maiese, and Wagner (1994)

found that a calcium-activated NO synthase is found in

several regions of the brain, including the dentate gyrus

and fields CA1 and CA3 of the hippocampus. Arancio et

al. (1995) obtained evidence that NO acts by stimulating

the production of cyclic GMP, a second messenger, in

presynaptic terminals. Although there is good evidence

that NO is one of the signals the dendritic spine uses to

communicate with the terminal button, most investigators

believe that there must be other signals as well. After all,

alterations in synapses require coordinated changes in

both presynaptic and postsynaptic elements.

For several years after its discovery, researchers

believed that LTP involved a single process. Since then

it has become clear that LTP consists of several stages.

**FIGURE 13.12** ■ **Role of CaM-KII in .**

**Long-Term Potentiation .**

CaM-KII molecules migrate into the postsynaptic densities of

dendritic spines after long-term potentiation. (a) A single

hippocampal pyramidal neuron is stained for the presence of

CaM-KII, before NMDA receptor stimulation. (b) The same

neuron after NMDA receptor stimulation. (c) An enlargement

of the area in (a) is marked by a white rectangle. The presence

of CaM-KII is shown in green. (d) An enlargement of the area

in (b) is marked by a white rectangle. The presence of CaM-KII

that has moved into dendritic spines is shown in red.

(From Shen, K., and Meyer, T. *Science,* 1999, *284,* 162–166. Copyright ©

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(a) (b)

(c) (d)

**FIGURE 13.13** ■ **Dendritic Spines in .**

**Field CA1 .**

According to Bourne and Harris (2007), long-term

potentiation may convert thin spines into mushroom-shaped

spines. (a) Colorized photomicrograph: Dendrite shafts are

yellow, spine necks are blue, spine heads are green, and

presynaptic terminals are orange. (b) Three-dimensional

reconstruction of a portion of a dendrite (yellow) shows the

variation I size and shape of postsynaptic densities (red).

(From Bourne, J., and Harris, K. M. *Current Opinion in Neurobiology,* 2007,

*17,* 381–386. Reprinted with permission.)

(a)

(b)

**nitric oxide synthase** An enzyme responsible for the production

of nitric oxide.

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**FIGURE 13.14** ■ **Growth of Dendritic Spines After .**

**Long-Term Potentiation .**

Two-photon microscopic images show a segment of a dendrite of a CA1 pyramidal neuron

before and after electrical stimulation that established long-term potentiation. Numbers in

each box indicate the time before or after the stimulation.

(From Nägerl, U. V., Köstinger, G., Anderson, J. C., Martin, K. A. C., and Bonhoeffer, T. *Journal of Neuroscience,*

2007, *27,* 8149–8156. Reprinted with permission.)

–0.5h +2h +21h

*Long-lasting* LTP—that is, LTP that lasts more than a

few hours—requires protein synthesis. Frey et al.

(1988) found that drugs that block protein synthesis

prevented the establishment of long-lasting LTP in field

CA1. If the drug was administered before, during, or

immediately after a prolonged burst of stimulation was

delivered, LTP occurred, but it disappeared a few hours

later. However, if the drug was administered one hour

after the synapses had been stimulated, the LTP persisted.

Apparently, the protein synthesis necessary for establishing

the later phase of long-lasting LTP is accomplished

within an hour of stimulation.

According to Raymond (2007), there are actually

three types of LTP. The first type, LTP1, involves almost

immediate changes in synaptic strength caused by

insertion of AMPA receptors. This form of LTP lasts for

an hour or two. The second type, LTP2, involves local

protein synthesis. Dendrites contain messenger RNAs

that can be translated into proteins. These RNAs

include codes for various enzymes, components of

receptors, and structural proteins (Martin and Zukin,

2006). The most durable type of long-term potentiation,

LTP3, involved production of mRNA in the nucleus

that is then transported to the dendrites, where protein

synthesis takes place. The long-lasting form of LTP

also requires the presence of dopamine, which stimulates

D1 receptors present on the dendrites. The importance

of dopamine in the establishment of long-term

memories is discussed later in this chapter.

For several years, investigators were puzzled about

the mechanism that controlled the location of the protein

synthesis initiated by production of mRNA in the

nucleus. As we saw, LTP involves individual synapses:

Only the synapses that are activated when the postsynaptic

membrane is depolarized are strengthened.

What mechanism delivers proteins produced in the cell

body by translation of newly produced mRNA to the

appropriate dendritic spines?

Evidence suggests that LTP initiates two processes:

the production of plasticity-related proteins through

normal synthesis of messenger RNA in the nucleus of

the cell and the production of a chemical “tag” in the

dendritic spines where the LTP has taken place. The

new proteins then diffuse throughout the dendrites of

the cell and are captured by the tags and used to stabilize

temporary synaptic changes and establish the

longest-lasting LTP (U. Frey and Morris, 1997; Frey and

Frey, 2008). (See ***Figure 13.15.***)

Figure 13.16 summarizes the biochemistry discussed

in this subsection. I suspect that you might feel

overwhelmed by all the new terms I have introduced

here, and I hope that the figure will help to clarify

things. The evidence we have seen so far indicates that

activation of a terminal button releases glutamate, which

binds with NMDA receptors in the postsynaptic membrane

of the dendritic spine. If this membrane was depolarized

by a dendritic spike, then calcium ions will enter

through channels controlled by the NMDA receptors

and activate CaM-KII, a calcium-dependent protein

kinase. CaM-KII travels to the postsynaptic density of

dendritic spines, where it causes the insertion of AMPA

receptors into the postsynaptic density. In addition, LTP

initiates rapid changes in synaptic structure and the production

of new synapses. (See ***Figure 13.16.***) The entry of

calcium also activates a calcium-dependent NO synthase,

and the newly produced NO then presumably diffuses

out of the dendritic spine, back to the terminal button.

There, it may trigger unknown chemical reactions that

increase the release of glutamate. (See ***Figure 13.16.***)

Finally, long-lasting LTP (LTP2 and LTP3) requires the

presence of dopamine and local and remote synthesis of

new proteins that stabilize the

changes made in the structure

of the potentiated synapse.

(See ***MyPsychKit 13.3, Chemistry***

***of LTP.***)

Animation 13.3

Chemistry of LTP

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**452 Chapter 13** Learning and Memory

Long-Term Depression

I mentioned earlier that low-frequency stimulation of

the synaptic inputs to a cell can *decrease* rather than

increase their strength. This phenomenon, known as

**long-term depression (LTD),** also plays a role in learning.

Apparently, neural circuits that contain memories

are established by strengthening some synapses and

weakening others. Dudek and Bear (1992) stimulated

Schaffer collateral inputs to CA1 neurons in hippocampal

slices with 900 pulses of electrical current,

delivered at rates ranging from 1 to 50 Hz. They found

that frequencies above 10 Hz caused long-term potentiation,

whereas those below 10 Hz caused long-term

depression. Both of these effects were blocked by application

of AP5, the NMDA receptor blocker; thus, both

effects require the activation of NMDA receptors. (See

***Figure 13.17.***)

Several studies have demonstrated *associative* longterm

depression, which is produced when synaptic

inputs are activated at the same time that the postsynaptic

membrane is either weakly depolarized or hyperpolarized

(Debanne, Gähwiler, and Thompson, 1994;

Thiels et al., 1996).

As we saw, the most commonly studied form of longterm

potentiation involves an increase in the number of

AMPA receptors in the postsynaptic membrane of dendritic

spines. Long-term depression appears to involve

the opposite: a *decrease* in the number of AMPA receptors

in these spines (Carroll et al., 1999). And just as

AMPA receptors are inserted into dendritic spines during

LTP, they are removed from the spines in vesicles

during LTD (Lüscher et al., 1999).

In field CA1, long-term depression, like long-term

potentiation, involves the activation of NMDA receptors,

and its establishment is disrupted by AP5. How can

activation of the same receptor produce opposite

effects? An answer was suggested by Lisman (1989),

who noted that sustained, low-frequency stimulation of

synapses on pyramidal cells in this region that produces

LTD would cause a modest but prolonged increase in

**FIGURE 13.15** ■ **The “Tag” Hypothesis of Frey and Morris (1998) .**

This hypothesis suggests how proteins, whose synthesis is initiated by synapses that are

undergoing long-term potentiation, can be directed to the locations where they are needed

to sustain long-lasting long-term potentiation.

Carlson/ POB,9e/C9B13F07.ai

20.0 x 15.4

LTP being

established

at this synapse After LTP is

established, the

chemical "tags"

are produced

Message is sent to

nucleus to produce

protein

Proteins are captured

by "tags," which trigger

the establishment of

long-lasting LTP

Molecules of protein

from nucleus

**long-term depression (LTD)** A long-term decrease in the

excitability of a neuron to a particular synaptic input caused by

stimulation of the terminal button while the postsynaptic

membrane is hyperpolarized or only slightly depolarized.

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**FIGURE 13.16** ■ **Chemistry of Long-Term .**

**Potentiation .**

These chemical reactions appear to be triggered by the entry

of an adequate amount of calcium into the dendritic spine.

Terminal

button

Enzyme Second

messenger

Increased

glutamate

release?

Ca2+

Ca2+

NMDA

receptor

AMPA

receptor

Dendritic

spine NO synthase

Arginine NO

Activation and

autophosphorylation

of CAM-KII

Insertion of additional

AMPA receptors into

the membrane

**FIGURE 13.17** ■ **Long-Term Potentiation .**

**and Long-Term Depression .**

The graph shows changes in the sensitivity of synapses of

Schaffer collateral axons with CA1 pyramidal cells after

electrical stimulation at various frequencies.

(Adapted from Dudek, S. M., and Bear, M. F. *Proceedings of the National*

*Academy of Sciences,* 1992, *89,* 4363–4367.)

20

10

0

–10

–20

1 3 5 10 50

Long-term potentiation

Long-term depression

Frequency of stimulation of

Schaffer collateral axons (Hz)

Percent change in slope of EPSP

intracellular Ca2+, whereas the intense, high-frequency

stimulation that produces LTP would cause a much

greater increase in Ca2+. Perhaps small and large

increases in intracellular calcium ions trigger different

mechanisms.

Evidence in favor of this hypothesis was obtained

by a study by Liu et al. (2004). NMDA receptors come

in at least two forms. One form contains one type of

subunit, and the other contains a different type of subunit.

Liu and his colleagues found that LTP was prevented

by a drug that blocked one type of NMDA

receptor and that LTD was prevented by a drug that

blocked the other type of NMDA receptor. Receptors

that produce LTP permit an influx of large amounts of

Ca2+ if they are stimulated repeatedly in a short amount

of time. In contrast, receptors that produce LTD permit

less calcium to enter the cell, but if they are stimulated

slowly over a long period of time, they permit the

buildup of a modest but prolonged increase in intracellular

calcium.

Other Forms of

Long-Term Potentiation

Long-term potentiation was discovered in the hippocampal

formation and has been studied more in this

region than in others, but it also occurs in many other

regions of the brain. Later in this chapter we will see the

role of LTP in particular forms of learning. In some but

not all of these regions, LTP is initiated by stimulation of

NMDA receptors. For example, in the hippocampal formation,

NMDA receptors are present in highest concentrations

in field CA1 and in the dentate gyrus. However,

very few NMDA receptors are found in the region of

field CA3 that receives mossy fiber input from the

dentate gyrus (Monaghan and Cotman, 1985). Highfrequency

stimulation of the mossy fibers produces LTP

that gradually decays over a period of several hours

(Lynch et al., 1991). AP5, the drug that blocks NMDA

receptors and prevents the establishment of LTP in CA1

neurons, has no effect on LTP in field CA3. In addition,

long-term potentiation in field CA3 appears to involve

only presynaptic changes; no alterations are seen in the

structure of dendritic spines after LTP has taken place

(Reid et al., 2004).

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PERCEPTUAL LEARNING

Learning enables us to adapt to our environment and to

respond to changes in it. In particular, it provides us

with the ability to perform an appropriate behavior in

an appropriate situation. Situations can be as simple as

the sound of a buzzer or as complex as the social interactions

of a group of people. The first part of learning

involves learning to perceive particular stimuli.

Perceptual learning involves learning to *recognize*

things, not *what to do* when they are present. (Learning

what to do is discussed in the next three sections of this

chapter.) Perceptual learning can involve learning to

recognize entirely new stimuli, or it can involve learning

to recognize changes or variations in familiar stimuli.

For example, if a friend gets a new hairstyle or replaces

glasses with contact lenses, our visual memory of that

person changes. We also learn that particular stimuli are

found in particular locations or contexts or in the presence

of other stimuli. We can even learn and remember

particular *episodes:* sequences of events taking place at a

particular time and place. The more complex forms of

perceptual learning will be discussed in the last section

of this chapter, which is devoted to relational learning.

Learning to Recognize Stimuli

In mammals with large and complex brains, objects are

recognized visually by circuits of neurons in the visual association

cortex. Visual learning can take place very rapidly,

and the number of items that can be remembered is enormous.

In fact, Standing (1973) showed people 10,000

color slides and found that they could recognize most of

the slides weeks later. Other primates are capable of

remembering items that they have seen for just a few seconds,

and the experience changes the responses of neurons

in their visual association cortex (Rolls, 1995b).

**InterimSummary**

**Synaptic Plasticity: Long-Term**

**Potentiation and Long-Term Depression**

The study of long-term potentiation in the hippocampal formation

has suggested a mechanism that might be responsible

for at least some of the synaptic changes that occur during

learning. A circuit of neurons passes from the entorhinal

cortex through the hippocampal formation. High-frequency

stimulation of the axons in this circuit strengthens synapses;

it leads to an increase in the size of the EPSPs in the dendritic

spines of the postsynaptic neurons. Associative long-term

potentiation can also occur, in which weak synapses are

strengthened by the action of strong ones. In fact, the only

requirement for LTP is that the postsynaptic membrane be

depolarized at the same time that the synapses are active.

In field CA1, in the dentate gyrus, and in several other

parts of the brain, NMDA receptors play a special role in LTP.

These receptors, sensitive to glutamate, control calcium

channels but can open them only if the membrane is already

depolarized. Thus, the combination of membrane depolarization

(for example, from a dendritic spike produced by the

activity of strong synapses) and activation of an NMDA receptor

causes the entry of calcium ions. The increase in calcium

activates several calcium-dependent enzymes, including

CaM-KII. CaM-KII causes the insertion of AMPA receptors into

the membrane of the dendritic spine, increasing their sensitivity

to glutamate released by the terminal button. This

change is accompanied by structural alterations in the shape

of the dendritic spine and by the growth of new spines,

which establish new synapses. LTP may also involve presynaptic

changes, through the activation of NO synthase, an

enzyme responsible for the production of nitric oxide. This

soluble gas may diffuse into nearby terminal buttons, where

it facilitates the release of glutamate. Long-lasting LTP

requires protein synthesis. The presence of “tag” molecules in

potentiated dendritic spines may capture proteins produced

in the soma and incorporate them into the synapse.

Long-term depression occurs when a synapse is activated

at the time that the postsynaptic membrane is hyperpolarized

or only slightly depolarized. In field CA1, LTP and LTD are established

by slightly different forms of NMDA receptors. If LTP and

LTD occurred only in the hippocampal formation, their discovery

would still be an interesting finding, but the fact that they

also occur in several other regions of the brain suggests that

they play an important role in many forms of learning.

**Thought Question**

The brain is the most complex organ in the body, and it is

also the most malleable. Every experience leaves at least a

small trace, in the form of altered synapses. When we tell

someone something or participate in an encounter that the

other person will remember, we are (literally) changing connections

in the person’s brain. How many synapses change

each day? What prevents individual memories from becoming

confused?

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**FIGURE 13.18** ■ **The Major Divisions of .**

**the Visual Cortex of the Rhesus Monkey .**

The arrows indicate the primary direction of the flow of

information in the dorsal and ventral streams.

Inferior temporal

cortex

Extrastriate

cortex

Posterior parietal

cortex

Primary visual

cortex

Ventral

Stream

Dorsal

Stream

As we saw in Chapter 6, the primary visual cortex

receives information from the lateral geniculate nucleus

of the thalamus. After the first level of analysis the information

is sent to the extrastriate cortex, which surrounds

the primary visual cortex (striate cortex). After

analyzing particular attributes of the visual scene, such

as form, color, and movement, subregions of the extrastriate

cortex send the results of their analysis to the next

level of the visual association cortex, which is divided

into two “streams.” The *ventral stream,* which is involved

with object recognition, continues ventrally into the inferior

temporal cortex. The *dorsal stream*, which is involved

with perception of the location of objects, continues dorsally

into the posterior parietal cortex. As some investigators

have said, the ventral stream is involved with the

*what* of visual perception, and the dorsal stream is

involved with the *where.* (See ***Figure 13.18.***)

Many studies have shown that lesions that damage

the inferior temporal cortex—part of the ventral

stream—disrupt the ability to discriminate between different

visual stimuli. These lesions impair the ability to

perceive (and thus to learn to recognize) particular

kinds of visual information. As we saw in Chapter 6, people

with damage to the inferior temporal cortex may

have excellent vision but be unable to recognize familiar,

everyday objects such as scissors, clothespins, or light

bulbs—and faces of friends and relatives.

Perceptual learning clearly involves changes in

synaptic connections in the visual association cortex that

establish new neural circuits—changes such as the ones

described in the previous section of this chapter. At a

later time, when the same stimulus is seen again and the

same pattern of activity is transmitted to the cortex,

these circuits become active again. This activity constitutes

the recognition of the stimulus—the readout of

the visual memory, so to speak. For example, Yang and

Maunsell (2004) trained monkeys to detect small differences

in visual stimuli whose images were projected

onto a specific region of the retina. After the training

was complete, the monkeys were able to detect differences

much smaller than those they could detect when

the training first started. However, they were unable to

detect these differences when the patterns were projected

onto other regions of the retina. Recordings of

single neurons in the visual association cortex showed

that the response properties of neurons that received

information from the “trained” region of the retina—

but not from other regions—had become sensitive to

small differences in the stimuli. Clearly, neural circuits

in that region alone had been modified by the training.

Let’s look at some evidence from studies with

humans that supports the conclusion that activation of

neural circuits in the sensory association cortex constitutes

the “readout” of a perceptual memory. Many years

ago, Penfield and Perot (1963) discovered that when

they stimulated the visual and auditory association cortex

as patients were undergoing seizure surgery, the patients

reported memories of images or sounds—for example,

images of a familiar street or the sound of the patient’s

mother’s voice. (You will recall from the opening case in

Chapter 3 that seizure surgery is performed under a

local anesthetic so that the surgeons can test the effects of

brain stimulation on the patients’ cognitive functions.)

Damage to regions of the brain involved in visual perception

not only impair the ability to recognize visual stimuli

but also disrupt people’s memory of the visual properties

of familiar stimuli. For example, Vandenbulcke et al.

(2006) found that Patient J. A., who had sustained damage

to the right fusiform gyrus, performed poorly on tasks that

required her to draw or describe visual features of various

animals, fruits, vegetables, tools, vehicles, or pieces of furniture.

Her other cognitive abilities, including the ability

to describe nonvisual attributes of objects, were normal. In

addition, an fMRI study found that when normal control

subjects were asked to perform the visual tasks that she

performed poorly, activation was seen in the region of

their brains that corresponded to J. A.’s lesion.

Kourtzi and Kanwisher (2000) found that specific

kinds of visual information can activate very specific

regions of visual association cortex. As we saw in

Chapter 6, a region of the visual association cortex,

MT/MST, plays an essential role in perception of movement.

The investigators presented subjects with photographs

that implied motion—for example, an athlete

getting ready to throw a ball. They found that photographs

like these, but not photographs of people

remaining still, activated area MT/MST. Obviously, the

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photographs did not move, but presumably, the subjects’

memories contained information about movements

they had previously seen. (See ***Figure 13.19.***)

A functional-imaging study by Goldberg, Perfetti, and

Schneider (2006) asked people questions that involved

visual, auditory, tactile, and gustatory information. The

researchers found that answering the questions activated

the regions of association cortex involved in perception of

the relevant sensory information. For example, questions

about flavor activated the gustatory cortex, questions

about tactile information activated the somatosensory cortex,

and questions about visual and auditory information

activated the visual and auditory association cortex.

Perceptual Short-Term Memory

So far, all the studies I have mentioned involved recognition

of stimuli, either particular objects or their locations.

Often, recognition is all that is necessary: We see

a stimulus and immediately make the appropriate

response. But sometimes the situation demands that we

make the appropriate response after a delay, even after

the stimulus is no longer visible. For example, suppose

that we have driven into a large parking lot, and because

we will have to carry a heavy package, we want to park as

near as possible to the entrance of a store located just in

front of us. We look to the left and see a space about

100 feet away. We then look to the right and see a space

about 50 feet away. Mentally comparing the distances,

we turn to the right. Because we could not look in both

directions simultaneously, we had to compare the distance

to the second space with our memory of the distance

to the first one. In other words, we had to compare

a perception with a short-term memory of something

else we had just perceived. A **short-term memory**

is the memory of a stimulus or an event that lasts for a

short while—usually on the order of a few seconds.

As we just saw, learning to recognize a stimulus

involves synaptic changes in the appropriate regions of

the sensory association cortex that establish new circuits

of neurons. *Recognition* of a stimulus occurs when sensory

input activates these established sets of neural circuits.

Short-term memory of a stimulus involves activity of

these circuits—or other circuits that are activated by

them—that continues even after the stimulus disappears.

For example, *learning* to recognize a friend’s face

produces changes in synaptic strengths in neural circuits

in the fusiform face region of our visual association

cortex, *recognizing* that she is present involves activation

of the circuits that are established by these changes, and

*remembering* that she is still in the room even when we

look elsewhere involves continued activity of these circuits

(or other circuits connected to them).

Functional-imaging studies have shown that retention

of specific types of short-term visual memories

involves activity of specific regions of the visual association

cortex. One region of the ventral stream, the *fusiform*

*face area,* is involved in recognition of faces, and another

region, the *parahippocampal place area,* is involved in recognition

of places. A functional-imaging study by Ranganath,

DeGutis, and D’Esposito (2004) found evidence that

short-term memory for particular faces and places was

associated with neural activity in two different regions of

the ventral stream of the visual association cortex. The

investigators trained people on a delayed matching-tosample

task that required them to remember particular

faces or places for a short period of time. In a **delayed**

**matching-to-sample task,** a subject is shown a stimulus

(the sample), and then, after a delay, the subject must

indicate which of several alternatives is the same as the

sample. Ranganath and his colleagues found that shortterm

memories of faces activated the fusiform face area

and that short-term memories of places activated the

parahippocampal place area. (See ***Figure 13.20.***)

**FIGURE 13.19** ■ **Evidence of Retrieval of .**

**Visual Memories of Movement .**

The bars represent the level of activation, measured by

fMRI, of MT/MST, a region of the visual association cortex

that responds to movement. Subjects looked at photographs

of static scenes or scenes that implied motion similar to the

ones shown here.

(Adapted from Kourtzi, A. and Kanwisher, N. *Journal of Cognitive*

*Neuroscience,* 2000, *12,* 48–55.)

1

1.5

0.5

2

2.5

Implied motion No implied

motion

At rest

Percent change in signal

**short-term memory** Memory of a stimulus or an event that lasts

for a short while.

**delayed matching-to-sample task** A task that requires the subject

to indicate which of several stimuli has just been perceived.

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**FIGURE 13.20** ■ **Short-Term Perceptual .**

**Memory .**

The fusiform face area and parahippocampal place area are

activated by information about faces or places in short-term

memory during cue and delay periods of a delayed

matching-to-sample task.

(Adapted from Ranganath, C., DeGutis, J., and D’Esposito, M. *Cognitive*

*Brain Research,* 2004, *20,* 37–45.)

Scene greater

than face

Face greater

than scene

Fusiform face area

Parahippocampal

place area

Cue Delay

Task period

Relative activation

**InterimSummary**

**Perceptual Learning**

Perceptual learning occurs as a result of changes in synaptic

connections within the sensory association cortex. Damage

to the inferior temporal cortex—the highest level of the ventral

stream of the visual association cortex—disrupts visual

As we saw in Chapter 6, transcranial magnetic stimulation

(TMS) of the visual association cortex interferes

with visual perception. TMS induces a weak electrical current

in the brain that disrupts neural activity and thus

interferes with the normal functions of the stimulated

region. Oliveri et al. (2001) trained people on a delayed

matching-to-sample task that required them to remember

either abstract figures or the locations of a white square on

a video screen. On some trials the investigators applied

TMS to the association cortex of either the ventral stream

or the dorsal stream during the delay interval, after the

sample stimuli had been turned off. They found that stimulating

the ventral stream interfered with short-term

memory for visual patterns and stimulating the dorsal

stream interfered with short-term memory for location.

Although the neural circuits responsible for learning

to recognize particular stimuli appear to reside in

the sensory association cortex, perceptual short-term

memories involve other brain regions as well—especially

the prefrontal cortex. Miyashita (2004) suggests that the

role of the prefrontal cortex in short-term memory is to

“manipulate and organize to-be-remembered information,

devise strategies for retrieval, and also monitor the

outcome” of these processes.

An example of this role was seen in a functionalimaging

study by Blumenfeld and Ranganarh (2006).

The investigators presented subjects with groups of

three words arranged vertically. The words were names

of animals or tangible objects, such as *owl*, *pillow*, and

*skunk*. Above each set of three words was a heading that

said REHEARSE or REORDER. In the REHEARSE condition

the subjects attempted to remember the words by

simply rehearsing them subvocally—silently saying the

words to themselves. In the REORDER condition the

subjects were told to rearrange the three words according

to the relative weights of the items they denoted. For

example, if the three words were “spider, tank, jar,” they

should remember them as “spider, jar, tank.” After a

delay, one of the words that had just been seen was presented

along with a number, and the subjects had to

indicate whether or not the number indicated the location

of the word in the sequence. For example, “tank”

would be in position 2 after the words “spider, tank, jar”

had been rearranged according to weight.

Blumenfeld and Ranganarh found that the dorsolateral

prefrontal cortex was activated during REORDER

trials. In fact, when the subjects were tested later, after

they left the scanner, they were most likely to remember

words from REORDER trials that were accompanied by

the greatest amount of activity in this brain region.

perceptual learning. Functional-imaging studies with

humans have shown that retrieval of memories of pictures,

sounds, movements, or spatial locations activates the appropriate

regions of the sensory association cortex.

Perceptual short-term memory involves sustained

activity of neurons in the sensory association cortex.

Functional-imaging studies have shown that retention of

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**458 Chapter 13** Learning and Memory

CLASSICAL CONDITIONING

Neuroscientists have studied the anatomy and physiology

of classical conditioning using many models, such as the

gill withdrawal reflex in *Aplysia* (a marine invertebrate)

and the eyeblink reflex in the rabbit (Carew, 1989;

Lavond, Kim, and Thompson, 1993). I have chosen to

describe a simple mammalian model of classical

conditioning—the conditioned emotional response—

to illustrate the results of such investigations.

The amygdala is part of an important system involved

in a particular form of stimulus-response learning: classically

conditioned emotional responses. An aversive stimulus

such as a painful foot shock produces a variety of

behavioral, autonomic, and hormonal responses: freezing,

increased blood pressure, secretion of adrenal stress

hormones, and so on. A classically conditioned emotional

response is established by pairing a neutral stimulus

(such as a tone of a particular frequency) with an aversive

stimulus (such as a brief foot shock). As we saw in Chapter

11, after these stimuli are paired, the tone becomes a CS;

when it is presented by itself, it elicits the same type of

responses as the unconditional stimulus does.

A conditioned emotional response can occur in the

absence of the auditory cortex (LeDoux et al., 1984);

thus, I will confine my discussion to the subcortical components

of this process. Information about the CS (the

tone) reaches the lateral nucleus of the amygdala. This

nucleus also receives information about the US (the

foot shock) from the somatosensory system. Thus, these

two sources of information converge in the lateral

nucleus, which means that synaptic changes responsible

for learning could take place in this location.

A hypothetical neural circuit is shown in Figure

13.21. The lateral nucleus of the amygdala contains neurons

whose axons project to the central nucleus.

Terminal buttons from neurons that transmit auditory

and somatosensory information to the lateral nucleus

form synapses with dendritic spines on these neurons.

When a rat encounters a painful stimulus, somatosensory

input activates strong synapses in the lateral nucleus. As

a result, the neurons in this nucleus begin firing, which

activates neurons in the central nucleus, evoking an

unlearned (unconditional) emotional response. If a tone

is paired with the painful stimulus, the weak synapses in

the lateral amygdala are strengthened through the action

of the Hebb rule. (See ***Figure 13.21.***)

This hypothesis has a considerable amount of support.

Lesions of the lateral nucleus of the amygdala disrupt

conditioned emotional responses that involve a

simple auditory stimulus as a CS and a shock to the feet

as a US (Kapp et al., 1979; Nader et al., 2001). Thus, the

synaptic changes responsible for this learning may take

place within this circuit.

specific types of short-term visual memories involves activity

of specific regions of the visual association cortex.

Transcranial magnetic stimulation of various regions of the

human sensory association cortex disrupt short-term perceptual

memories. The prefrontal cortex is also involved in

short-term memory. This region encodes information pertaining

to the stimulus that must be remembered and is

involved in manipulating and organizing information in

short-term memory.

**Thought Questions**

1. How many perceptual memories does your brain hold?

How many images, sounds, and odors can you recognize,

and how many objects and surfaces can you recognize by

touch? Is there any way we could estimate these quantities?

2. Can you think of times when you saw something that

you needed to remember and did so by keeping in mind

a response you would need to make rather than an

image of the stimulus you just perceived?

**FIGURE 13.21** ■ **Conditioned Emotional .**

**Responses .**

The figure shows the probable location of the changes in

synaptic strength produced by the classically conditioned

emotional response that results from pairing a tone with a

foot shock.

Tone

(CS)

Aversive

stimulus

(US) Strong

synapse

Central

nucleus

Conditioned

emotional

responses:

hypothalamus,

midbrain, pons,

and medulla

Basal

nucleus

Synapse

strengthened

by pairing of

CS and US

Lateral

nucleus

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**Classical Conditioning 459**

**FIGURE 13.22** ■ **Classical Conditioning .**

**in the Lateral Amygdala .**

The graph shows the change in rate of firing of neurons in

the lateral amygdala in response to the tone, relative to

baseline levels.

(Adapted from Quirk, G. J., Repa, J. C., and LeDoux, J. E. *Neuron,* 1995, *15,*

1029–1039.)

0

1 2 3 4 5 6

Conditioning Extinction

200

400

600

Percent of change

Blocks of 10 trials

**InterimSummary**

**Classical Conditioning**

You have already encountered the conditioned emotional

response in Chapter 11 and in the previous section of this

chapter, in which I discussed perceptual learning. When an

auditory stimulus (CS) is paired with a foot shock (US), the two

types of information converge in the lateral nucleus of the

amygdala. This nucleus is connected, directly and via the

basal nucleus and accessory basal nucleus, with the central

Quirk, Repa, and LeDoux (1995) found evidence

for synaptic changes in the lateral nucleus of the amygdala.

They recorded the activity of neurons in this nucleus

in freely moving rats before, during, and after pairing of

a tone with a foot shock. Within a few trials the neurons

became more responsive to the tone, and many neurons

that had not previously responded to the tone began

doing so. When they repeatedly presented the tone

without the foot shock, the response extinguished, and

the rate of firing of the neurons in the lateral nucleus

returned to baseline levels. (See ***Figure 13.22.***) Maren

(2000) confirmed these results and also found that the

magnitude of the increased firing rate of neurons in the

lateral nucleus correlated with the magnitude of the

conditioned emotional response.

The evidence from many studies indicates that the

changes in the lateral amygdala responsible for acquisition

of a conditioned emotional response involve

LTP. LTP in many parts of the brain—including the

amygdala—is accomplished through the activation of

NMDA receptors. Rodrigues, Schafe, and LeDoux

(2001) used a drug that blocks the NR2B subunit of

the NMDA receptor. The investigators found that infusion

of this drug into the lateral amygdala prevented

the acquisition of a conditioned emotional response.

Injections of drugs that block LTP into the amygdala

prevent the establishment of conditioned emotional

responses.

Rumpel et al. (2005) used a harmless virus to insert

a gene for a fluorescent dye coupled to a subunit of the

AMPA receptor into the lateral amygdala of rats. They

paired a tone with a shock and established a conditioned

emotional response. They found that the learning

experience caused AMPA receptors to be driven into

dendritic spines of synapses between lateral amygdala

neurons and axons that provide auditory input. The

investigators also inserted a gene for a fluorescent dye

coupled with a defective subunit of the AMPA receptor

into the lateral amygdala. The defective subunit prevented

AMPA receptors from being driven into the dendritic

spines. As a result, conditioning did not take

place. In fact, infusion of a wide variety of drugs into the

lateral amygdala that prevent long-term potentiation in

this nucleus disrupt acquisition of a conditioned emotional

response (Rodrigues, Schafe, and LeDoux, 2004;

Schafe et al., 2005; Schafe, Doyère, and LeDoux, 2005).

The results of these studies support the conclusion that

LTP in the lateral amygdala, mediated by NMDA receptors,

plays a critical role in the establishment of conditioned

emotional responses.

nucleus, which is connected with brain regions that control

various components of the emotional response. Lesions anywhere

in this circuit disrupt the response.

Recordings of single neurons in the lateral nucleus of the

amygdala indicate that classical conditioning changes the

response of neurons to the CS. The mechanism of synaptic

plasticity in this system appears to be NMDA-mediated longterm

potentiation. Infusion of drugs that block LTP into the

lateral nucleus blocks establishment of conditioned emotional

responses.

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INSTRUMENTAL

CONDITIONING

Instrumental (operant) conditioning is the means by

which we (and other animals) profit from experience.

If, in a particular situation, we make a response that has

favorable outcomes, we will tend to make the response

again. This section first describes the neural pathways

involved in instrumental conditioning and then discusses

the neural basis of reinforcement.

Basal Ganglia

As we saw earlier in this chapter, instrumental conditioning

entails the strengthening of connections between

neural circuits that detect a particular stimulus and neural

circuits that produce a particular response. Clearly,

the circuits that are responsible for instrumental conditioning

begin in various regions of the sensory association

cortex, where perception takes place, and end in

the motor association cortex of the frontal lobe, which

controls movements. But what pathways are responsible

for these connections, and where do the synaptic

changes responsible for the learning take place?

There are two major pathways between the sensory

association cortex and the motor association cortex:

direct transcortical connections (connections from one

area of the cerebral cortex to another) and connections

via the basal ganglia and thalamus. (A third pathway,

involving the cerebellum and thalamus, also exists, but

the role of this pathway in instrumental conditioning

has until very recently received little attention from neuroscientists.)

Both of these pathways appear to be

involved in instrumental conditioning, but they play different

roles.

In conjunction with the hippocampal formation,

the transcortical connections are involved in the acquisition

of episodic memories—complex perceptual memories

of sequences of events that we witness or that are

described to us. (The acquisition of these types of memories

is discussed in the last section of this chapter.) The

transcortical connections are also involved in the acquisition

of complex behaviors that involve deliberation or

instruction. For example, a person learning to drive a

car with a manual transmission might say, “Let’s see,

push in the clutch, move the shift lever to the left and

then away from me—there, it’s in gear—now let the

clutch come up—oh! It died—I should have given it

more gas. Let’s see, clutch down, turn the key. . . .” A

memorized set of rules (or an instructor sitting next to

us) provides a script for us to follow. Of course, this

process does not have to be audible or even involve

actual movements of the speech muscles; a person can

think in words with neural activity that does not result in

overt behavior. (Animals that cannot communicate by

means of language can acquire complex responses by

observing and imitating the behavior of other animals.)

At first, performing a behavior through observation

or by following a set of rules is slow and awkward. And

because so much of the brain’s resources are involved in

recalling the rules and applying them to our behavior, we

cannot respond to other stimuli in the environment—we

must ignore events that might distract us. But then, with

practice, the behavior becomes much more fluid.

Eventually, we perform it without thinking and can easily

do other things at the same time, such as carrying on a

conversation with passengers as we drive our car.

Evidence suggests that as learned behaviors become

automatic and routine, they are “transferred” to the

basal ganglia. The process seems to work like this: As we

deliberately perform a complex behavior, the basal ganglia

receive information about the stimuli that are present

and the responses we are making. At first the basal

ganglia are passive “observers” of the situation, but as

the behaviors are repeated again and again, the basal

ganglia begin to learn what to do. Eventually, they take

over most of the details of the process, leaving the

transcortical circuits free to do something else. We need

no longer think about what we are doing.

The neostriatum—the caudate nucleus and the

putamen—receives sensory information from all regions

of the cerebral cortex. It also receives information from

the frontal lobes about movements that are planned or

are actually in progress. (So as you can see, the basal ganglia

have all the information they need to monitor the

progress of someone learning to drive a car.) The outputs

of the caudate nucleus and the putamen are sent to

another part of the basal ganglia: the globus pallidus. The

outputs of this structure are sent to the frontal cortex: to

the premotor and supplementary motor cortex, where

plans for movements are made, and to the primary motor

cortex, where they are executed. (See ***Figure 13.23.***)

Studies with laboratory animals have found that

lesions of the basal ganglia disrupt instrumental conditioning

but do not affect other forms of learning. For

example, Fernandez-Ruiz et al. (2001) destroyed the

portions of the caudate nucleus and putamen that

receive visual information from the ventral stream. They

found that although the lesions did not disrupt visual

perceptual learning, they impaired the monkeys’ ability

to learn to make a visually guided operant response.

Williams and Eskandar (2006) trained monkeys to

move a joystick in a particular direction (left, right, forward,

or backward) when they saw a particular visual

stimulus. Correct responses were reinforced with a sip of

fruit juice. As the monkeys learned the task, the rate of

firing of single neurons in the caudate nucleus

increased. In fact, the activity of caudate neurons was

correlated with the animals’ rate of learning. When the

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investigators increased the activation of caudate neurons

through low-intensity, high-frequency electrical stimulation

during the reinforcement period, they monkeys

learned a particular stimulus-response association more

quickly. These results provide further evidence for the

role of the basal ganglia in instrumental conditioning.

As we saw in the previous section, long-term potentiation

appears to play a critical role in classical conditioning.

This form of synaptic plasticity appears to be

involved in instrumental conditioning, as well. Packard

and Teather (1997) found that blocking NMDA receptors

in the basal ganglia with an injection of AP5 disrupted

learning guided by a simple visual cue.

Reinforcement

Learning provides a means for us to profit from

experience—to make responses that provide favorable

outcomes. When good things happen (that is, when

reinforcing stimuli occur), reinforcement mechanisms

in the brain become active, and the establishment of

synaptic changes is facilitated. The discovery of the existence

of such reinforcement mechanisms occurred by

accident.

Neural Circuits Involved

in Reinforcement

In 1954, James Olds, a young assistant professor, and

Peter Milner, a graduate student, attempted to determine

whether electrical stimulation of the reticular formation

would facilitate maze learning in rats. They

planned to turn on the stimulator briefly each time an

**FIGURE 13.23** ■ **The Basal Ganglia and .**

**Their Connections .**

Primary

somatosensory

cortex

Primary

motor cortex

Supplementary

motor area

Premotor

cortex Caudate nucleus

Putamen

Neostriatum

Globus pallidus,

internal

Subthalamic

nucleus

VA/VL thalamus

Globus pallidus,

external

animal reached a choice point in the maze. First, however,

they had to be certain that the stimulation was not aversive,

because an aversive stimulus would undoubtedly

interfere with learning. As Olds reported,

I applied a brief train of 60-cycle sine-wave electrical

current whenever the animal entered one

corner of the enclosure. The animal did not

stay away from that corner, but rather came

back quickly after a brief sortie which followed

the first stimulation and came back even more

quickly after a briefer sortie which followed the

second stimulation. By the time the third electrical

stimulus had been applied the animal

seemed indubitably to be “coming back for

more.” (Olds, 1973, p. 81)

Realizing that they were on to something big, Olds

and Milner decided to drop their original experiment

and study the phenomenon they had discovered.

Subsequent research discovered that although there are

several different reinforcement mechanisms, the activity

of dopaminergic neurons plays a particularly important

role in reinforcement. As we saw in Chapter 4, the

mesolimbic system of dopaminergic neurons begins in

the **ventral tegmental area (VTA)** of the midbrain and

projects rostrally to several forebrain regions, including

the amygdala, hippocampus, and **nucleus accumbens**

**(NAC).** This nucleus is located in the basal forebrain rostral

to the preoptic area and immediately adjacent to the

septum. (In fact, the full name of this region is the *nucleus*

*accumbens septi,* or “nucleus leaning against the septum.”)

(See ***Figure 13.24.***) Neurons in the NAC project to the

ventral part of the basal ganglia, which, as we just saw, are

involved in learning. The mesocortical system also plays a

role in reinforcement. This system also begins in the ventral

tegmental area but projects to the prefrontal cortex,

the limbic cortex, and the hippocampus.

Chapter 5 described a research technique called

*microdialysis,* which enables an investigator to analyze the

contents of the interstitial fluid within a specific region

of the brain. Researchers using this method have shown

that reinforcing electrical stimulation of the medial

forebrain bundle or the ventral tegmental area or the

administration of cocaine or amphetamine causes the

release of dopamine in the nucleus accumbens

(Moghaddam and Bunney, 1989; Nakahara et al., 1989;

Phillips et al., 1992). (The medial forebrain bundle

**ventral tegmental area (VTA)** A group of dopaminergic neurons

in the ventral midbrain whose axons form the mesolimbic and

mesocortical systems; plays a critical role in reinforcement.

**nucleus accumbens** A nucleus of the basal forebrain near the

septum; receives dopamine-secreting terminal buttons from

neurons of the ventral tegmental area and is thought to be

involved in reinforcement and attention.

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connects the ventral tegmental area with the nucleus

accumbens. See ***Figure 13.25.***) Microdialysis studies have

also found that the presence of natural reinforcers, such

as water, food, or a sex partner, stimulates the release of

dopamine in the nucleus accumbens. Thus, the effects

of reinforcing brain stimulation seem to be similar in

many ways to those of natural reinforcers.

Although microdialysis probes are not placed in the

brain of humans for experimental purposes, functionalimaging

studies have shown that reinforcing events activate

the human nucleus accumbens. For example,

Knutson et al. (2001) found that the nucleus accumbens

became more active (and, presumably, dopamine was

being released there) when people were presented with

stimuli that indicated that they would be receiving

money. Aharon et al. (2001) found that young heterosexual

men would press a lever that presented pictures

of beautiful women (but not handsome men) and that

when they saw these pictures, the activity of the nucleus

accumbens increased.

I should note that microdialysis studies have found

that aversive stimuli, as well as reinforcing stimuli, can

cause the release of dopamine in various parts of the

brain, including the nucleus accumbens (Salamone,

1992). Thus, it is clear that reinforcement is not the sole

function of dopaminergic neurons; these neurons

appear to be involved in stress as well. Also, because the

**FIGURE 13.24** ■ **The Ventral Tegmental Area and the .**

**Nucleus Accumbens .**

Diagrams of sections through a rat brain show the location of these regions.

(Adapted from Swanson, L. W. *Brain Maps: Structure of the Rat Brain.* New York: Elsevier, 1992.)

Corpus

callosum

Hippocampal

formation

Substantia

nigra

Ventral

tegmental

area

Nucleus

Anterior accumbens

commissure

Septal

area

Corpus

callosum

Basal

ganglia

**FIGURE 13.25** ■ **Dopamine and .**

**Reinforcement .**

Release of dopamine in the nucleus accumbens, measured

by microdialysis is produced when a rat pressed a lever that

delivered electrical stimulation to the ventral tegmental area.

(Adapted from Phillips, A. G., Coury, A., Fiorino, D., LePiane, F. G., Brown,

E., and Fibiger, H. C. *Annals of the New York Academy of Sciences,* 1992,

*654,* 199–206.)

450

400

350

300

250

200

150

100

0 30 60 90 120

Reinforcing

brain stimulation

Dopamine level (percentage of baseline)

Time (min)

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**FIGURE 13.26** ■ **Expected and Unexpected .**

**Reinforcers .**

The functional MRI scans show the effects of expected and

unexpected reinforcers (sips of fruit juice) on activity of the

nucleus accumbens (arrows) in humans.

(From Berns, G. S., McClure, S. M., Pagnoni, G., and Montague, P. R.

*Journal of Neuroscience,* 2001, *21,* 2793–2798. Reprinted with permission.)

Expected reward

Unexpected reward

stimulation of several regions of the brain is reinforcing,

the mesolimbic system is only one of several reinforcement

systems.

Functions of the Reinforcement System

A reinforcement system must perform two functions:

detect the presence of a reinforcing stimulus (that is,

recognize that something good has just happened) and

strengthen the connections between the neurons that

detect the discriminative stimulus (such as the sight of a

lever) and the neurons that produce the instrumental

response (a lever press). (Refer to ***Figure 13.2.***)

Assuming that this proposed mechanism is correct,

several questions remain: What activates the dopaminergic

neurons in the midbrain, causing their terminal buttons

to release dopamine? What role does the release of

dopamine play in strengthening synaptic connections?

Where do these synaptic changes take place? Research

that suggests some preliminary answers to these questions

is discussed in the rest of this section.

Detecting Reinforcing Stimuli. Reinforcement

occurs when neural circuits detect a reinforcing stimulus

and cause the activation of dopaminergic neurons in the

ventral tegmental area. Detection of a reinforcing stimulus

is not a simple matter; a stimulus that serves as a reinforcer

on one occasion may fail to do so on another. For

example, the presence of food will reinforce the behavior

of a hungry animal but not that of an animal that has

just eaten. Thus, the reinforcement system is not automatically

activated when particular stimuli are present;

its activation also depends on the state of the animal.

Studies by Schultz and his colleagues, recording the

activity of dopaminergic neurons in the nucleus accumbens,

have discovered that the reinforcement system

appears to be activated by *unexpected* reinforcing stimuli.

For example, Mirenowicz and Schultz (1994, 1996)

taught monkeys an operant task that required them to

make a response when they heard an auditory stimulus.

During training, dopaminergic neurons in the VTA

responded rapidly when the reinforcing stimulus (a tasty

liquid) was delivered. However, once the animals learned

the task, the VTA neurons became active when the auditory

stimulus was presented but not when the reinforcing

stimulus was delivered. In addition, if a reinforcing stimulus

does not occur when it is expected, the activity of

dopaminergic neurons suddenly decreases (Day et al.,

2007). A functional-imaging study by Berns et al. (2001)

found similar results with humans. Figure 13.26. shows

that when a small amount of tasty fruit juice was squirted

in people’s mouths unpredictably, the nucleus accumbens

was activated, but when the delivery of fruit juice was

predictable, no such activity occurred. (See ***Figure 13.26.***)

Schultz and his colleagues suggest that activation of

the dopaminergic neurons of the VTA tells other circuits

in the brain that an event that has informational value

with respect to a potentially reinforcing stimulus has just

occurred. In other words, the activity of these neurons

sends a signal that there is something to be learned. If

the delivery of the reinforcer is already expected, then

there is nothing that needs to be learned.

Under some conditions, novelty in itself appears to

activate dopaminergic neurons and facilitate long-term

potentiation and learning. For example, Li et al. (2003)

found that long-term potentiation could more easily be

established in field CA1 of rats that had just been briefly

exposed to a novel environment. A drug that blocked

dopamine receptors prevented this enhancement. A

functional-imaging study by Schott et al. (2004) investigated

the effect of novelty on learning in humans. In the

first part of the experiment, the subjects performed a

task that familiarized them with various configurations

of stimuli. Next, the subjects read words that were presented

along with either familiar or novel settings. The

novel settings activated the ventral tegmentum, and

when the subjects were later asked to recall the words,

they remembered more of the ones that had been presented

in the novel settings, when the dopaminergic

neurons of the midbrain appeared to be active.

A functional-imaging study by Knutson and Adcock

(2005) found that anticipation of a reinforcing stimulus

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(the opportunity to win some money) increased the activation

of the ventral tegmentum and some of its projection

regions (including the nucleus accumbens) in

humans. The investigators found that the subjects were

more likely to remember pictures that they had seen while

they were anticipating the chance to win some money.

As we have seen, the prefrontal cortex provides an

important input to the ventral tegmental area. The terminal

buttons of the axons connecting these two areas

secrete glutamate, an excitatory neurotransmitter, and

the activity of these synapses makes dopaminergic neurons

in the ventral tegmental area fire in a bursting

pattern, which greatly increases the amount of

dopamine they secrete in the nucleus accumbens

(Gariano and Groves, 1988). The prefrontal cortex is

generally involved in devising strategies, making plans,

evaluating progress made toward goals, and judging

the appropriateness of one’s own behavior. Perhaps

the prefrontal cortex turns on the reinforcement

mechanism when it determines that the ongoing

behavior is bringing the organism nearer to its goals—

that the present strategy is working.

Even private behaviors such as thinking and planning

may be subject to reinforcement. For example,

recall the last time you were thinking about a problem

and suddenly had an idea that might help you to solve

it. Did you suddenly feel excited and happy? It would be

interesting if we could record the activity of the axons

leading from your frontal cortex to your ventral tegmental

area at times like that.

Strengthening Neural Connections: Dopamine

and Neural Plasticity. Like classical conditioning,

instrumental conditioning involves strengthening of

synapses located on neurons that have just been active.

However, instrumental conditioning involves three elements:

a discriminative stimulus, a response, and a reinforcing

stimulus. How are the neural manifestations of

these three elements combined?

Let’s consider a hungry rat learning to press a lever

and obtain food. As in classical conditioning, one element

(the discriminative stimulus—in this case the sight

of the lever) activates only weak synapses on motor neurons

responsible for a movement that causes a lever

press. The second element—the particular circumstance

that happened to induce the animal to press the lever—

activates strong synapses, making the neurons fire. The

third element comes into play only if the response is followed

by a reinforcing stimulus. If it is, the reinforcement

mechanism triggers the secretion of a neurotransmitter

or neuromodulator throughout the region in

which the synaptic changes take place. This chemical

is the third element; only if it is present can weak

synapses be strengthened. Dopamine serves such a role.

Several studies have shown that long-term potentiation

is essential for instrumental conditioning and that

dopamine is an essential ingredient in long-lasting longterm

potentiation.

Smith-Roe and Kelley (2000) found that the presence

of dopamine and the activation of NMDA receptors

in the nucleus accumbens both appear to be necessary

for instrumental conditioning to take place. They

found that a low dose of a dopamine D1 receptor antagonist

or a low dose of AP5 into the nucleus accumbens

had no effect on rats’ ability to learn a lever-pressing

task. However, simultaneous infusion of the same doses

of the two drugs severely impaired the animals’ ability to

learn this task. Knecht et al. (2004) taught people a

vocabulary of artificial words. The learning took place

gradually, during five daily sessions. In a double-blind

procedure, some subjects were given L-DOPA 90 minutes

before each session, and others were given a placebo.

(As you know, L-DOPA is the precursor for dopamine,

and administration of this drug increases the release of

dopamine in the brain.) The subjects who received the

L-DOPA learned the artificial vocabulary faster and

remembered it better than those who received the

placebo.

As I mentioned earlier, the prefrontal cortex may

activate the reinforcement system when it detects that

the animal’s behavior is resulting in progress toward a

goal. But the prefrontal cortex is a *target* of dopaminergic

neurons as well as a source of their control. For

example, Stein and Belluzzi (1989) found that rats will

press a lever that produces an injection of a dopamine

agonist into this region. Duvauchelle and Ettenberg

(1991) found that if a rat’s prefrontal cortex is electrically

stimulated while the animal is in a particular location,

the animal will learn to prefer that location to

others where the stimulation did not take place. This

learning appears to involve the release of dopamine,

because it is prevented by injections of a drug that

blocks dopamine receptors. And in a microdialysis

study, Hernandez and Hoebel (1990) found that when

rats were performing a food-reinforced lever-pressing

task, the levels of dopamine in the prefrontal cortex

increased.

Dopamine modulates LTP in the prefrontal cortex

as well as in the nucleus accumbens. Gurden, Tassin,

and Jay (1999) found that stimulation of the VTA

enhanced LTP in the prefrontal cortex produced by

electrical stimulation of the hippocampus. Gurden,

Takita, and Jay (2000) found that infusion of D1 receptor

agonists into the prefrontal cortex did so as well but

that D1 antagonists impaired LTP. A study by Bissière,

Humeau, and Luthi (2003) found that dopamine facilitates

LTP in the lateral amygdala as well. These experiments

provide further evidence that dopamine plays a

modulating role in synaptic plasticity in parts of the

brain that are involved in learning.

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**InterimSummary**

**Instrumental Conditioning**

Instrumental conditioning entails the strengthening of connections

between neural circuits that detect stimuli and neural

circuits that produce responses. One of the locations of

these changes appears to be the basal ganglia, especially the

changes responsible for learning of automated and routine

behaviors. The basal ganglia receive sensory information and

information about plans for movement from the neocortex.

Instrumental conditioning activates the basal ganglia, and

damage to the basal ganglia or infusion of a drug that blocks

NMDA receptors there disrupts instrumental conditioning.

Olds and Milner discovered that rats would perform a

response that caused electrical current to be delivered through

an electrode placed in the brain; thus, the stimulation was

reinforcing. Subsequent studies found that stimulation of many

locations had reinforcing effects but that the medial forebrain

bundle produced the strongest and most reliable ones.

Although several neurotransmitters may play a role in

reinforcement, one is particularly important: dopamine. The

cell bodies of the most important system of dopaminergic

neurons are located in the ventral tegmental area, and their

axons project to the nucleus accumbens, prefrontal cortex,

and amygdala.

Microdialysis studies have also shown that natural and

artificial reinforcers stimulate the release of dopamine in the

nucleus accumbens, and functional-imaging studies have

shown that reinforcing stimuli activate the nucleus accumbens

in humans. The dopaminergic reinforcement system

appears to be activated by unexpected reinforcers or by stimuli

that predict the occurrence of a reinforcer. Conditions

such as novelty or the expectation of a reinforcing stimulus

facilitate learning. The prefrontal cortex may play a role in

reinforcement that occurs when our own behavior brings us

nearer to a goal.

Dopamine induces synaptic plasticity by facilitating

associative long-term potentiation. Evidence indicates that

dopamine can facilitate long-term potentiation in the nucleus

accumbens, amygdala, and prefrontal cortex.

**Thought Question**

Have you ever been working hard on a problem and suddenly

thought of a possible solution? Did the thought make

you feel excited and happy? What would we find if we had a

microdialysis probe in your nucleus accumbens?

RELATIONAL LEARNING

So far, this chapter has discussed relatively simple forms

of learning, which can be understood as changes in circuits

of neurons that detect the presence of particular

stimuli or as strengthened connections between neurons

that analyze sensory information and those that produce

responses. But most forms of learning are more complex;

most memories of real objects and events are related

to other memories. Seeing a photograph of an old friend

may remind you of the sound of the person’s name and

of the movements you have to make to pronounce it. You

may also be reminded of things you have done with your

friend: places you have visited, conversations you have

had, experiences you have shared. Each of these memories

can contain a series of events, complete with sights

and sounds, that you will be able to recall in the proper

sequence. Obviously, the neural circuits in the visual

association cortex that recognize your friend’s face are

connected to circuits in many other parts of the brain,

and these circuits are connected to many others. This

section discusses research on relational learning, which

includes the establishment and retrieval of memories of

events, episodes, and places.

Human Anterograde Amnesia

One of the most dramatic and intriguing phenomena

caused by brain damage is *anterograde amnesia,* which,

at first glance, appears to be the inability to learn new

information. However, when we examine the phenomenon

more carefully, we find that the basic abilities

of perceptual learning, stimulus-response learning,

and motor learning are intact but that complex

relational learning, of the type I just described, is

gone. This section discusses the nature of anterograde

amnesia in humans and its anatomical basis.

The section that follows discusses related research

with laboratory animals.

The term **anterograde amnesia** refers to difficulty in

learning new information. A person with pure anterograde

amnesia can remember events that occurred in

the past, from the time before the brain damage

occurred, but cannot retain information encountered

**anterograde amnesia** Amnesia for events that occur after some

disturbance to the brain, such as head injury or certain

degenerative brain diseases.

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*after* the damage. In contrast, **retrograde amnesia** refers

to the inability to remember events that happened *before*

the brain damage occurred. (See ***Figure 13.27.***) As we

will see, pure anterograde amnesia is rare; usually, there

is also a retrograde amnesia for events that occurred for

a period of time before the brain damage occurred.

In 1889, Sergei Korsakoff, a Russian physician, first

described a severe memory impairment caused by brain

damage, and the disorder was given his name. The most

profound symptom of **Korsakoff’s syndrome** is a severe

anterograde amnesia: The patients appear to be unable

to form new memories, although they can still remember

old ones. They can converse normally and can

remember events that happened long before their brain

damage occurred, but they cannot remember events that

happened afterward. As we will see in Chapter 15, the

brain damage that causes Korsakoff’s syndrome is usually

(but not always) a result of chronic alcohol abuse.

Anterograde amnesia can also be caused by damage

to the temporal lobes. Scoville and Milner (1957)

reported that bilateral removal of the medial temporal

lobe produced a memory impairment in humans that

was apparently identical to that seen in Korsakoff’s syndrome.

H. M., the man described in the case that

opened this chapter, received the surgery in an attempt

to treat his severe epilepsy, which could not be controlled

even by high doses of anticonvulsant medication.

The epilepsy appears to have been caused by a head

injury he received when he was struck by a bicycle at age

nine (Corkin et al., 1997).

The surgery successfully treated H. M.’s seizure disorder,

but it became apparent that the operation had

produced a serious memory impairment. Further investigation

revealed that the critical site of damage was the

hippocampus. Once it was known that bilateral medial

temporal lobectomy causes anterograde amnesia, neurosurgeons

stopped performing this operation and are

now careful to operate on only one temporal lobe.

H. M.’s history and memory deficits were described

in the introduction to this chapter (Milner, Corkin, and

Teuber, 1968; Milner, 1970; Corkin et al., 1981). Because

of his relatively pure amnesia, he has been extensively

studied. Milner and her colleagues based the following

conclusions on his pattern of deficits:

1. *The hippocampus is not the location of long-term memories;*

*nor is it necessary for the retrieval of long-term memories.*

If it were, H. M. would not have been able to

remember events from early in his life, he would

not know how to talk, he would not know how to

dress himself, and so on.

2. *The hippocampus is not the location of immediate (shortterm)*

*memories.* If it were, H. M. would not be able to

carry on a conversation, because he would not

remember what the other person said long enough

to think of a reply.

3. *The hippocampus is involved in converting immediate*

*(short-term) memories into long-term memories.* This conclusion

is based on a particular hypothesis of memory

function: that our immediate memory of an

event is retained by neural activity and that longterm

memories consist of relatively permanent biochemical

or structural changes in neurons. The

conclusion seems a reasonable explanation for

the fact that when presented with new information,

H. M. seems to understand it and remember it as

long as he thinks about it but that a permanent

record of the information is just never made.

As we will see, these three conclusions are too simple.

Subsequent research on patients with anterograde

amnesia indicates that the facts are more complicated—

and more interesting—than they first appeared to be.

But to appreciate the significance of the findings of

more recent research, we must understand these three

conclusions and remember the facts that led to them.

As we saw earlier in this chapter, most psychologists

believe that learning consists of at least two stages:

short-term memory and long-term memory. They conceive

of short-term memory as a means of storing a limited

amount of information temporarily and long-term

memory as a means of storing an unlimited amount (or

at least an enormously large amount) of information

permanently. We can remember a new item of information

(such as a telephone number) for as long as we

want by engaging in a particular behavior: rehearsal.

However, once we stop rehearsing the information, we

might or might not be able to remember it later; that is,

the information might or might not get stored in longterm

memory.

**retrograde amnesia** Amnesia for events that preceded some

disturbance to the brain, such as a head injury or electroconvulsive

shock.

**Korsakoff ’s syndrome** Permanent anterograde amnesia caused by

brain damage resulting from chronic alcoholism or malnutrition.

**FIGURE 13.27** ■ **A Schematic Definition .**

**of Retrograde Amnesia and .**

**Anterograde Amnesia .**

Retrograde

Amnesia

Anterograde

Amnesia

Cannot remember

events prior to

brain damage

Cannot later

remember events

that occur after

brain damage

Brain

damage

occurs

Time

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**FIGURE 13.29** ■ **Examples of Broken .**

**Drawings .**

(Reprinted with permission of author and publisher from Gollin, E. S.

Developmental studies of visual recognition of incomplete objects.

*Perceptual and Motor Skills,* 1960, *11,* 289–298.)

Set I

Set II

Set III

Set IIII

Set V

The simplest model of the memory process says that

sensory information enters short-term memory, rehearsal

keeps it there, and eventually, the information makes its

way into long-term memory, where it is permanently

stored. The conversion of short-term memories into

long-term memories has been called **consolidation,**

because the memories are “made solid,” so to speak.

(See ***Figure 13.28.***)

Now you can understand the original conclusions of

Milner and her colleagues: If H. M.’s short-term memory

is intact and if he can remember events from before his

operation, then the problem must be that consolidation

does not take place. Thus, the role of the hippocampal

formation in memory is consolidation—converting

short-term memories to long-term memories.

Spared Learning Abilities

H. M.’s memory deficit is striking and dramatic.

However, when he and other patients with anterograde

amnesia are studied more carefully, it becomes apparent

that the amnesia does not represent a total failure in

learning ability. When the patients are appropriately

trained and tested, we find that they are capable of three

of the four major types of learning described earlier in

this chapter: perceptual learning, stimulus-response

learning, and motor learning. A review by Spiers,

Maguire, and Burgess (2001) summarized 147 cases of

anterograde amnesia that are consistent with the

description that follows.

First, let us consider perceptual learning. Figure

13.29. shows two sample items from a test of the ability

to recognize broken drawings; note how the drawings

are successively more complete. (See ***Figure***

***13.29.***) Subjects are first shown the least complete set

(set I) of each of twenty different drawings. If they do

not recognize a figure (and most people do not recognize

set I), they are shown more complete sets until

they identify it. One hour later, the subjects are tested

again for retention, starting with set I. When H. M. was

given this test and was retested an hour later, he

showed considerable improvement (Milner, 1970).

When he was retested four months later, he *still*

showed this improvement. His performance was not

as good as that of normal control subjects, but he

showed unmistakable evidence of long-term retention.

(You can try the broken

drawing task and some other

tasks that people with anterograde

amnesia can successfully

learn by running ***MyPsychKit***

***13.4, Implicit Memory Tasks.***)

Johnson, Kim, and Risse (1985) found that

patients with anterograde amnesia could learn to recognize

faces. The researchers played unfamiliar

melodies from Korean songs to amnesic patients and

found that when they were tested later, the patients

preferred these melodies to ones they had not heard

before. The experimenters also presented photographs

of two men along with stories of their lives: One

man was said to be dishonest, mean, and vicious; the

other was said to be nice enough to invite home to dinner.

(Half of the patients heard that one of the men

was the bad one, and the other half heard that the

other man was.) Twenty days later, the amnesic patients

**FIGURE 13.28** ■ **A Simple Model of the .**

**Learning Process .**

Sensory

information

Short-term

memory

Long-term

memory

Rehearsal

Consolidation

Animation 13.4

Implicit Memory Tasks

**consolidation** The process by which short-term memories are

converted into long-term memories.

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said they liked the picture of the “nice” man better

than that of the “nasty” one.

Investigators have also succeeded in demonstrating

stimulus-response learning by H. M. and other amnesic

subjects. For example, Woodruff-Pak (1993) found that

H. M. and another patient with anterograde amnesia

could acquire a classically conditioned eyeblink

response. H. M. even showed retention of the task two

years later: He acquired the response again in one-tenth

the number of trials that were needed previously.

Sidman, Stoddard, and Mohr (1968) successfully

trained patient H. M. on an instrumental conditioning

task—a visual discrimination task in which pennies were

given for correct responses.

Finally, several studies have demonstrated motor

learning in patients with anterograde amnesia. For

example, Reber and Squire (1998) found that subjects

with anterograde amnesia could learn a sequence of button

presses in a *serial reaction time task*. They sat in front of

a computer screen and watched an asterisk appear—

apparently randomly—in one of four locations. Their

task was to press the one of four buttons that corresponded

to the location of the asterisk. As soon as they

did so, the asterisk moved to a new location, and they

pressed the corresponding button. (See ***Figure 13.30.***)

Although experimenters did not say so, the

sequence of button presses specified by the moving

asterisk was not random. For example, it might be

DBCACBDCBA, a ten-item sequence that is repeated

continuously. With practice, subjects become faster and

faster at this task. It is clear that their rate increases

because they have learned the sequence, because if the

sequence is changed, their performance decreases. The

amnesic subjects learned this task just as well as normal

subjects did.

A study by Cavaco et al. (2004) tested amnesic

patients on a variety of tasks modeled on real-world

activities, such as weaving, tracing figures, operating a

stick that controlled a video display, and pouring water

into small jars. Both amnesic patients and normal subjects

did poorly on these tasks at first, but their performance

improved through practice. Thus, as you can see,

patients with anterograde amnesia are capable of a variety

of tasks that require perceptual learning, stimulusresponse

learning, and motor learning.

Declarative and Nondeclarative

Memories

If amnesic patients can learn tasks like these, you

might ask, why do we call them *amnesic*? The answer is

this: Although the patients can learn to perform these

tasks, they do not remember anything about having

learned them. They do not remember the experimenters,

the room in which the training took place,

the apparatus that was used, or any events that

occurred during the training. Although H. M. learned

to recognize the broken drawings, he denied that he

had ever seen them before. Although the amnesic

patients in the study by Johnson, Kim, and Risse

learned to like some of the Korean melodies better,

they did not recognize that they had heard them

before; nor did they remember having seen the pictures

of the two young men. Although H. M. successfully

acquired a classically conditioned eyeblink response,

he did not remember the experimenter, the apparatus,

or the headband he wore that held the device that

delivered a puff of air to his eye.

In the experiment by Sidman, Stoddard, and Mohr,

although H. M. learned to make the correct response

(press a panel with a picture of a circle on it), he was

unable to recall having done so. In fact, once H. M. had

learned the task, the experimenters interrupted him,

had him count his pennies (to distract him for a little

while), and then asked him to say what he was supposed

to do. He seemed puzzled by the question; he had

absolutely no idea. But when they turned on the stimuli

again, he immediately made the correct response.

Finally, although the amnesic subjects in Reber and

Squire’s study obviously learned the sequence of button

presses, they were completely unaware that there was,

in fact, a sequence; they thought that the movement of

the asterisk was random.

The distinction between what people with anterograde

amnesia can and cannot learn is obviously

important because it reflects the basic organization of

the learning process. Clearly, there are at least two

major categories of memories. Psychologists have given

them several different names. For example, some

investigators (Eichenbaum, Otto, and Cohen, 1992;

**FIGURE 13.30** ■ **The Serial Reaction .**

**Time Task .**

In the procedure of the study by Reber and Squire (1998),

subjects pressed the button in a sequence indicated by

movement of the asterisk on the computer screen.

A B C D

\*

DBCACBDCBA

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Squire, 1992) suggest that patients with anterograde

amnesia are unable to form **declarative memories,**

which have been defined as those that are “explicitly

available to conscious recollection as facts, events, or

specific stimuli” (Squire, Shimamura, and Amaral,

1989, p. 218). The term *declarative* obviously comes

from *declare,* which means “to proclaim; to announce.”

The term reflects the fact that patients with anterograde

amnesia cannot talk about experiences that they

have had since the time of their brain damage. Thus,

according to Squire and his colleagues, declarative

memory is memory of events and facts that we can

think and talk about.

Declarative memories are not simply verbal memories.

For example, think about some event in your life,

such as your last birthday. Think about where you were,

when the event occurred, what other people were present,

what events occurred, and so on. Although you

could describe (“declare”) this episode in words, the

memory itself would not be verbal. In fact, it would

probably be more like a video clip running in your head,

one whose starting and stopping points—and fast forwards

and rewinds—you could control.

The other category of memories, often called

**nondeclarative memories,** includes instances of perceptual,

stimulus-response, and motor learning that we are

not necessarily conscious of. (Some psychologists refer

to these two categories as *explicit* and *implicit* memories,

respectively.) Nondeclarative memories appear to operate

automatically. They do not require deliberate

attempts on the part of the learner to memorize something.

They do not seem to include facts or experiences;

instead, they control behaviors. For example,

think about when you learned to ride a bicycle. You did

so quite consciously and developed declarative memories

about your attempts: who helped you learn, where

you rode, how you felt, how many times you fell, and

so on. But you also formed nondeclarative stimulusresponse

and motor memories; *you learned to ride.* You

learned to make automatic adjustments with your

hands and body that kept your center of gravity above

the wheels.

The acquisition of specific behaviors and skills is

probably the most important form of implicit memory.

Driving a car, turning the pages of a book, playing a

musical instrument, dancing, throwing and catching a

ball, sliding a chair backward as we get up from the dinner

table—all of these skills involve coordination of

movements with sensory information received from the

environment and from our own moving body parts. We

do not need to be able to describe these activities in

order to perform them. We may not even be aware of all

the movements we make while we are performing them.

Patient E. P. developed a profound anterograde

amnesia when he was stricken with a case of viral

encephalitis that destroyed much of his medial temporal

lobe. Bayley, Frascino, and Squire (2005) taught

patient E. P. to point to a particular member of each

of a series of eight pairs of objects. He eventually

learned to do so, but he had no explicit memory of

which objects were correct. When asked why he chose

a particular object, he said, “It just seems that’s the

one. It’s here (pointing to head) somehow or another

and the hand goes for it. . . . I can’t say memory. I just

feel this is the one. . . . It’s just jumping out at me. ‘I’m

the one. I’m the one’” (Bayley, Frascino, and Squire,

2005, p. 551). Clearly, he learned a nondeclarative

stimulus-response task without at the same time

acquiring any declarative memories about what he

had learned.

What brain regions are responsible for the acquisition

of nondeclarative memories? As we saw earlier in

this chapter, perceptual memories involve the sensory

regions of the cerebral cortex. The basal ganglia appear

to play an essential role in stimulus-response and motor

learning. Several experiments have shown that people

with diseases of the basal ganglia have deficits that can

be attributed to difficulty in learning automatic

responses. For example, Owen et al. (1992) found that

patients with Parkinson’s disease were impaired on

learning a visually cued instrumental conditioning task,

and Willingham and Koroshetz (1993) found that

patients with Huntington’s disease failed to learn a

sequence of button presses. (Parkinson’s disease and

Huntington’s disease are both degenerative diseases of

the basal ganglia.)

Table 13.1 lists the declarative and nondeclarative

memory tasks that I have described so far. (See

***Table 13.1.***)

Anatomy of Anterograde Amnesia

The phenomenon of anterograde amnesia—and its

implications for the nature of relational learning—

has led investigators to study this phenomenon in laboratory

animals. But before I review this research

(which has provided some very interesting results),

we should examine the brain damage that produces

anterograde amnesia. One fact is clear: Damage to

the hippocampus or to regions of the brain that supply

its inputs and receive its outputs causes anterograde

amnesia.

**declarative memory** Memory that can be verbally expressed, such

as memory for events in a person’s past.

**nondeclarative memory** Memory whose formation does not

depend on the hippocampal formation; a collective term for

perceptual, stimulus-response, and motor memory.

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As we saw earlier in this chapter, the hippocampal

formation consists of the dentate gyrus, the CA fields

of the hippocampus itself, and the subiculum (and its

subregions). The most important input to the hippocampal

formation is the entorhinal cortex; neurons

there have axons that terminate in the dentate

gyrus, CA3, and CA1. The entorhinal cortex receives

its inputs from the amygdala, various regions of the

limbic cortex, and all association regions of the

neocortex, either directly or via two adjacent regions

of limbic cortex: the **perirhinal cortex** and the

**parahippocampal cortex.** Collectively, these three

regions constitute the *limbic cortex of the medial temporal*

*lobe.* (See ***Figure 13.31.***)

The outputs of the hippocampal system come primarily

from field CA1 and the subiculum. Most of these

outputs are relayed back through the entorhinal,

perirhinal, and parahippocampal cortex to the same

regions of association cortex that provide inputs.

The hippocampal formation also receives input

from subcortical regions via the fornix. These inputs

select and modulate the functions of the hippocampal

formation. The fornix carries dopaminergic axons

from the ventral tegmental area, noradrenergic axons

from the locus coeruleus, serotonergic axons from

the raphe nuclei, and acetylcholinergic axons from

the medial septum. The fornix also connects the

**perirhinal cortex** A region of limbic cortex adjacent to the

hippocampal formation that, along with the parahippocampal

cortex, relays information between the entorhinal cortex and other

regions of the brain.

**parahippocampal cortex** A region of limbic cortex adjacent to the

hippocampal formation that, along with the perirhinal cortex,

relays information between the entorhinal cortex and other regions

of the brain.

**TABLE 13.1** ■ **Examples of Declarative and Nondeclarative Memory Tasks .**

DECLARATIVE MEMORY TASKS

Remembering past experiences

Finding one’s way in new environment

NONDECLARATIVE MEMORY TASKS TYPE OF LEARNING

Learning to recognize broken drawings Perceptual

Learning to recognize pictures and objects Perceptual

Learning to recognize faces Perceptual (and stimulus-response?)

Learning to recognize melodies Perceptual

Classical conditioning (eyeblink) Stimulus-response

Instrumental conditioning (choose circle) Stimulus-response

Learning sequence of button presses Motor

hippocampal formation with the mammillary bodies,

located in the posterior hypothalamus. The most

prominent brain damage seen in cases of Korsakoff’s

syndrome—and presumably the cause of the anterograde

amnesia—is degeneration of the mammillary

bodies. (See ***Figure 13.32.***)

The clearest evidence that damage restricted to

the hippocampal formation produces anterograde

amnesia came from a case studied by Zola-Morgan,

Squire, and Amaral (1986). Patient R. B., a 52-yearold

man with a history of heart trouble, sustained a

cardiac arrest. Although his heart was successfully

restarted, the period of anoxia caused by the temporary

halt in blood flow resulted in brain damage. The

primary symptom of this brain damage was permanent

anterograde amnesia, which Zola-Morgan and

his colleagues carefully documented. Five years after

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the onset of the amnesia, R. B. died of heart failure.

His family gave permission for histological examination

of his brain.

The investigators discovered that field CA1 of the

hippocampal formation was gone; its neurons had completely

degenerated. Subsequent studies reported other

patients with anterograde amnesia caused by CA1 damage

(Victor and Agamanolis, 1990; Kartsounis, Rudge, and

Stevens, 1995; Rempel-Clower et al., 1996). (See ***Figure***

***13.33.***) In addition, several studies have found that a

period of anoxia causes damage to field CA1 in monkeys

and in rats and that the damage causes anterograde

amnesia in these species too (Auer, Jensen, and

Whishaw, 1989; Zola-Morgan et al., 1992).

Why is field CA1 of the hippocampus so sensitive to

anoxia? The answer appears to lie in the fact that this

region is especially rich in NMDA receptors. For some

reason, metabolic disturbances of various kinds, including

seizures, anoxia, or hypoglycemia, cause glutamatergic

terminal buttons to release glutamate at

abnormally high levels. The effect of this glutamate

release is to stimulate NMDA receptors, which permit

the entry of calcium. Within a few minutes, excessive

amounts of intracellular calcium begin to destroy the

neurons. If animals are pretreated with drugs that block

NMDA receptors, a period of anoxia is much less likely

to produce brain damage (Rothman and Olney, 1987).

CA1 neurons contain many NMDA receptors, so longterm

potentiation can quickly become established

there. This flexibility undoubtedly contributes to our

ability to learn as quickly as we do. But it also renders

these neurons particularly susceptible to damage by

metabolic disturbances.

Role of the Hippocampal

Formation in Consolidation

of Declarative Memories

As we saw earlier in this chapter, the hippocampus is

not the location of either short-term or long-term memories;

after all, patients with damage to the hippocampal

formation can remember events that happened

before the brain became damaged, and their shortterm

memory is relatively normal. But the hippocampal

formation clearly plays a role in the process through

which declarative memories are formed. Most

researchers believe that the process works something

like this: The hippocampus receives information about

what is going on from sensory and motor association

cortex and from some subcortical regions, such as the

basal ganglia and amygdala. It processes this information

and then, through its *efferent* connections with

these regions, modifies the memories that are being

consolidated there, linking them together in ways that

will permit us to remember the relationships among

the elements of the memories—for example, the order

in which events occurred, the context in which we perceived

a particular item, and so on. Without the hippocampal

formation we would be left with individual,

isolated memories without the linkage that makes it

possible to remember—and think about—episodes and

contexts.

**FIGURE 13.31** ■ **Cortical Connections of .**

**the Hippocampal Formation .**

The figure shows (a) a view of the base of a monkey’s brain

and (b) connections with the cerebral cortex.

Hippocampus Amygdala

Limbic cortex

of the medial

temporal lobe

Parahippocampal

cortex

Entorhinal

cortex

Perirhinal

cortex

(a)

Hippocampus

Parahippocampal

cortex

Entorhinal

cortex

Perirhinal

cortex

(b)

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If the hippocampus does modify memories as they

are being formed, then experiences that lead to declarative

memories should activate the hippocampal formation.

In fact, several studies have found this prediction

to be true. In general, pictorial or spatial information

activates the right hippocampal formation, and verbal

information activates the left hippocampal formation.

For example, Brewer et al. (1998) had normal subjects

look at a series of complex color photos and later tested

their ability to say whether they remembered them. (As

we saw, people with anterograde amnesia are capable of

perceptual learning, but they cannot *say* whether they

have seen a particular item.) While the subjects were

studying the pictures the first time, the experimenters

recorded regional brain activity by functional MRI.

Brewer and his colleagues found that the pictures that

the subjects were most likely to remember later were

those that caused the most activation of the right

hippocampal region, suggesting that this region was

involved in the encoding phase of memory formation. A

study by Alkire et al. (1998) found that activation of the

*left* hippocampal formation was related to a person’s

**FIGURE 13.33** ■ **Damage to Field CA1 Caused by Anoxia .**

The scans show (a) section through a normal hippocampus and (b) section through the

hippocampus of patient G. D. The pyramidal cells of field CA1 (between the two

arrowheads) have degenerated. (DG = dentate gyrus, gl, ml, pl = layers of the dentate

gyrus, PaS = parasubiculum, PrS = presubiculum, S = subiculum.)

(From Rempel-Clower, N. L., Zola, S. M., Squire, L. R., and Amaral, D. G. *Journal of Neuroscience,* 1996, *16,*

5233–5255. Reprinted with permission.)

(a) (b)

**FIGURE 13.32** ■ **The Major Subcortical Connections of the .**

**Hippocampal Formation .**

A midsagittal view of a rat brain shows these connections.

Hippocampal

formation Cingulate cortex

Acetylcholinergic

input

Dopaminergic

Noradrenergic input

input

Serotonergic

input

Medial

septum

Amygdala

MMB

Ventral

tegmental

Locus area

Raphe coeruleus

nuclei

Thalamus

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ability to remember a list of words: The subjects with the

greatest amount of activation showed the best memory

for the words. (See ***Figure 13.34.***)

As we saw, anterograde amnesia is usually accompanied

by retrograde amnesia—the inability to remember

events that occurred for a period of time before the

brain damage occurred. The duration of the retrograde

amnesia appears to be related to the amount of

damage to the medial temporal lobe (Squire and

Bayley, 2007; Kirwan et al., 2008). Damage limited to

the hippocampus (including the dentate gyrus and

subiculum) results in a retrograde amnesia lasting a few

years. Additional damage to the entorhinal cortex produces

a retrograde amnesia of one to two decades.

Damage that involves the hippocampus and much of

the medial temporal lobe produces a retrograde amnesia

that spares only those memories from early life. The

memories that are spared in all these cases include

semantic memories acquired early in life, memories of

personal episodes when the patient was younger, and

the ability to navigate in or describe the early home

neighborhood.

The following examples illustrate retrieval of early

memories by a patient with a profound anterograde

amnesia.

**FIGURE 13.34** ■ **The Hippocampal .**

**Formation and Encoding of .**

**Declarative Memories .**

(a) The scan shows regions whose metabolic activity during

learning correlated with likelihood of recall later. “Hot”

colors reflect positive correlations; “cool” colors reflect

negative correlations. The arrow points to the hippocampal

formation. (b) The graph shows the percentage correct during

free recall as a function of relative metabolic rate of the left

hippocampal formation of the nine subjects in the study.

(Adapted from Alkire, M. T., Haier, R. J., Fallon, J. H., and Cahill, L. *Proceedings*

*of the National Academy of Sciences, USA,* 1998, 95, 14506–14510.)

Relative metabolic rate

of left hippocampal formation

Free recall (percent correct)

20

40

60

80

100

0

0 0.2 0.4 0.6 0.8 1.0 1.2 1.4

(b)

(a)

Patient E. P. made the following response when he was asked

to describe an incident from the period before he attended

school.

When I was 5 years old, we moved from Oakland to

the country. I was very excited and looked forward

to the change. I remember the truck that dad rented.

It was hardly full because we didn’t have much

furniture. When it was time to leave, mom got in the

car and followed behind the truck. I rode in the

truck with dad. (Reed and Squire, 1998, p. 3951)

Patient E. P. is also able to find his way around the neighborhood

where he grew up but is completely lost in the

neighborhood to which he moved after he became amnesic

(Teng and Squire, 1999).

The fact that retrograde amnesia extends back for

a limited period of time suggests that a gradual process

controlled by the hippocampal formation transforms

memories located elsewhere. Before this transformation

is complete, the hippocampal formation is

required for the retrieval of these memories. Later,

retrieval of these memories can be accomplished even

if the hippocampal formation has been damaged. A

functional-imaging study by Takashima et al. (2006)

supports this hypothesis. The investigators had normal

subjects look at 320 different photographs of landscapes

for 5.5 seconds each. The subjects were encouraged

to try to memorize the photographs. For example,

the investigators gave the subjects specific examples of

learning strategies, such as “‘Where on the picture

would you like to be most?’, ‘Where do you think the

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place is?’, and ‘Look for very special, distinct objects on

the picture’” (p. 759). Later that day, one day later, one

month later, and three months later, the investigators

presented photographs that included a mixture of new

photographs and a sample of the photographs the subjects

had previously seen and asked the subjects to identify

which ones were familiar to them. A different sample

of previously seen photographs was presented at

each session, which meant that the memories for the

initial set of 320 photographs got progressively older.

The subjects brains were scanned during each memorytesting

session.

Takashima and her colleagues found that initially,

the degree of hippocampal activation correlated with

the subjects’ memory of the photographs they had

previously seen. However, as time went on, the hippocampal

activation decreased, and the activation of

the prefrontal cortex showed a correlation with correct

identification. (See ***Figure 13.35.***) The investigators

concluded that the hippocampus played a role in

retrieval of early memories but that this task was transferred

to the prefrontal cortex as time went on. They

suggest that it is unlikely that the memories for the

photographs were stored in the prefrontal cortex but

hypothesized that this region, with its rich connections

with other regions of the cerebral cortex, might

be involved in organizing and linking information

stored elsewhere.

You might wonder why the hippocampus would be

involved in a perceptual memory in the first place. After

all, we saw earlier that people with hippocampal damage

can learn to recognize visual stimuli. The answer is that

when people with anterograde amnesia are shown

images that they had previously seen (but after the onset

of their amnesia), they will deny having seen them

before. However, if they are given a forced choice

between an old image and a new one, they will point to

the one they had previously seen, without showing any

signs of real recognition. You will recall that patient E. P.

said, “I can’t say memory. I just feel this is the one. . . .

It’s just jumping out at me” (Bayley, Frascino, and

Squire, 2005, p. 551). This nondeclarative perceptual

memory is different from the declarative memory that

the subjects in the study by Takashima et al., who

–0.75

–0.50

–0.25

0

0.25

0.50

0.75

–0.4

–0.2

0

0.2

0.4

0.6

0.8

Relative activity Relative activity

1 30 60 90

1 30 60 90

Time

Ventromedial prefrontal cortex

Hippocampus

(days)

**FIGURE 13.35** ■ **Changing Roles of Hippocampus and .**

**Prefrontal Cortex in Memory .**

The role of the ventromedial prefrontal cortex (top) increased over time, and the role of

the hippocampus (bottom) decreased over time.

(From Takashima, A., Petersson, K. M., Rutters, F., Tendolkar, I., Jensen, O., Zwarts, M. J., McNaughton, B. L.,

and Fernández, G. *Proceedings of the National Academy of Sciences, USA,* 2006, *103,* 756–761. Reprinted with

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deliberately encouraged their subjects to think about

the photographs and try to remember them.

You might also wonder why the role of the hippocampus

in maintaining access to a memory appears

to end in less than three months, whereas retrograde

amnesia caused by hippocampal damage lasts for at least

several years. The most likely explanation is that when

investigators test for the extent of a patient’s retrograde

amnesia, they ask questions about more complex memories,

such as autobiographical episodes, which involve

sequences of many individual memories. Retrieval of

such complex sets of memories may require the participation

of the hippocampus for a much longer time.

Episodic and Semantic Memories

Evidence suggests that semantic and episodic memories

are distinct forms of declarative memory. **Episodic memories**

involve context; they include information about

when and under what conditions a particular episode

occurred and the order in which the events in the

episode took place. Episodic memories are specific to a

particular time and place, because a given episode—by

definition—occurs only once. **Semantic memories**

involve facts, but they do not include information about

the context in which the facts were learned. In other

words, semantic memories are less specific than episodic

memories. For example, knowing that the sun is a star

involves a less specific memory than being able to remember

when, where, and from whom you learned this fact.

Semantic memories can be acquired gradually, over time.

Episodic memories must be learned all at once.

Acquisition of both major categories of declarative

memories—episodic and semantic—appears to require

the participation of the hippocampus. Manns, Hopkins,

and Squire (2003) found that five patients with damage

limited to the hippocampal formation showed an

anterograde amnesia for semantic as well as episodic

information.

As we saw earlier in this chapter, perceptual memories

appear to be located in the sensory association cortex,

the regions where the perceptions take place.

Presumably, episodic memories, which consist of an integrated

sequence of perceptual memories, are also located

there. What about semantic memories—memories for

factual information? Knowing that the sun is a star certainly

involves memories different from knowing what

the sun looks like. Thus, semantic memories are not simply

perceptual memories. A degenerative neurological

disorder known as **semantic dementia** suggests that the

temporal lobe plays an important role in storing semantic

information. Semantic dementia is caused by degeneration

of the neocortex of the anterolateral temporal

lobe (Lambon Ralph and Patterson, 2008). At least in the

early stages of the degenerative process the hippocampal

formation and the rest of the medial temporal lobe are

not affected. Murre, Graham, and Hodges (2001)

describe the case of patient A. M., born in 1930 and studied

by the investigators between 1994 and 1997.

**episodic memory** Memory of a collection of perceptions of events

organized in time and identified by a particular context.

**semantic memory** A memory of facts and general information.

**semantic dementia** Loss of semantic memories caused by

progressive degeneration of the neocortex of the lateral temporal

lobes.

A. M. was an active, intelligent man who had received an

undergraduate degree in engineering and a master’s degree

in science. He worked for an internationally renowned company,

where he was responsible for managing over 450

employees. His neurological symptoms began with progressive

difficulty in understanding the speech of others and

finding appropriate words of his own. By the time Murre and

his colleagues met A. M., his speech was fluent and grammatical

but contained little meaning.

Examiner: Can you tell me about a time you were in

hospital?

A. M.: Well one of the best places was in April last

year here (ha ha) and then April, May, June, July,

August, September and then October, and then

April today.

Examiner: Can you remember April last year?

A. M.: April last year, that was the first time, and eh,

on the Monday, for example, they were checking all

my whatsit, and that was the first time, when my

brain was, eh, shown, you know, you know that bar

of the brain (indicates left), not the, the other one

was okay, but that was lousy, so they did that and

then doing everything like that, like this and probably

a bit better than I am just now (indicates scanning

by moving his hands over his head). (Murre,

Graham, and Hodges, 2001, p. 651)

Patient A. M.’s loss of semantic information had a profound

effect on his everyday activities. He seemed not to

understand functions of commonplace objects. For example,

he held a closed umbrella horizontally over his head during

a rainstorm and brought his wife a lawnmower when she had

asked for a stepladder. He put sugar into a glass of wine and

put yogurt on a raw defrosting salmon steak and ate it. He

nevertheless showed some surprisingly complex behaviors.

Because he could not be trusted to drive a car, his wife surreptitiously

removed the car keys from his key ring. He

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As you can see, the symptoms of semantic dementia

are quite different from those of anterograde amnesia.

Semantic information is lost, but episodic memory for

recent events can be spared. The hippocampal formation

and the limbic cortex of the medial temporal lobe

appear to be involved in the consolidation and retrieval

of declarative memories, both episodic and semantic,

but the semantic memories themselves appear to be

stored in the neocortex—in particular, in the neocortex

of the anterolateral temporal lobe. Pobric, Jefferies, and

Lambon Ralph (2007) found that transcranial magnetic

stimulation of the left anterior temporal lobe, which disrupted

the normal neural activity of this region, produced

the symptoms of semantic dementia. The subjects

had difficulty naming pictures of objects and

understanding the meanings of words, but they had no

trouble performing other, nonsemantic, tasks such as

naming six-digit numbers and matching large numbers

according to their approximate size. Also, a functionalimaging

study by Rogers et al. (2006) recorded activation

of the anterolateral temporal lobes when people

performed a picture-naming task.

Spatial Memory

I mentioned earlier in this chapter that patient H. M.

has not been able to find his way around his present

environment. Although spatial information need not be

declared (we can demonstrate our topographical memories

by successfully getting from place to place), people

with anterograde amnesia are unable to consolidate

information about the location of rooms, corridors,

buildings, roads, and other important items in their

environment.

Bilateral medial temporal lobe lesions produce the

most profound impairment in spatial memory, but significant

deficits can be produced by damage that is limited

to the right hemisphere. For example, Luzzi et al.

(2000) reported the case of a man with a lesion of the

right parahippocampal gyrus who lost his ability to find

his way around a new environment. The only way he

could find his room was by counting doorways from the

end of the hall or by seeing a red napkin that was located

on top of his bedside table.

Functional-imaging studies have shown that the

right hippocampal formation becomes active when a

person is remembering or performing a navigational

task. For example Maguire, Frackowiak, and Frith (1997)

had London taxi drivers describe the routes they would

take in driving from one location to another. Functional

imaging that was performed during their description of

the route showed activation of the right hippocampal

formation. London taxi drivers undergo extensive training

to learn how to navigate efficiently in that city; in fact,

this training takes about two years, and the drivers

receive their license only after passing a rigorous set of

tests. We would expect that this topographical learning

would produce some changes in various parts of their

brains, including their hippocampal formation. In fact,

Maguire et al. (2000) found that the volume of the posterior

hippocampus of London taxi drivers was larger

than that of control subjects. Furthermore, the longer an

individual taxi driver had spent in this occupation, the

larger was the volume of the right posterior hippocampus.

As we will see later in this chapter, the dorsal hippocampus

of rats (which corresponds to the posterior

hippocampus of humans) contains *place cells*—neurons

that are directly involved in navigation in space.

Other experiments provides further evidence for

the role of the hippocampus in spatial memory. Hartley

et al. (2003) trained subjects to find their way in a computerized

virtual-reality town. Some subjects became

acquainted with the town by exploring it, giving them

the opportunity to learn where various landmarks

(shops, cafés, etc.) were located with respect to each

other. Other subjects were trained to follow a specific

pathway from one landmark to the next, making a

sequence of turns to get from a particular starting point

to another. The investigators hypothesized that the first

task, which involved spatial learning, would require the

participation of the hippocampus, while the second

task, which involved learning a set of specific responses

to a set of specific stimuli, would require the participation

of the basal ganglia. The results were as predicted:

Functional MRI revealed that the spatial task activated

the hippocampus and the response task activated the

caudate nucleus (a component of the basal ganglia).

Iaria et al. (2003) used a similar task that permitted

subjects to learn a maze either through distant spatial

cues or through a series of turns. About half of the subjects

spontaneously used spatial cues, and the other half

spontaneously learned to make a sequence of responses

at specific locations. Again, fMRI showed the hippocampus

was activated in subjects who followed the *spatial*

*strategy* and the caudate nucleus was activated in subjects

noticed their absence, and rather than complaining to her

(presumably, he realized that would be fruitless), he surreptitiously

removed the car keys from her key ring, went to a

locksmith, and had a duplicate set made.

Although his semantic memory was severely damaged,

his episodic memory was surprisingly good. The investigators

reported that even when his dementia had progressed to the

point at which he was scoring at chance levels on a test of

semantic information, he answered a phone call that was

meant for his wife, who was out of the house. When she

returned later, he remembered to tell her about the call. ISBN 0-558-46775-X

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who followed the *response strategy*. In addition, a structural

MRI study by Bohbot et al. (2007) found that people

who tended to follow a spatial strategy in a virtual maze

had a larger-than-average hippocampus, and people

who tended to follow a response strategy had a largerthan-

average caudate nucleus. (You will recall that the

caudate nucleus, part of the basal ganglia, plays a role in

stimulus-response learning.) Figure 13.36. shows the

relationship between performance on test trials that

could be performed only by using a response strategy.

As you can see, the larger a person’s caudate nucleus is

(and the smaller a person’s hippocampus is), the fewer

errors that person made. (See ***Figure 13.36.***)

Relational Learning in

Laboratory Animals

The discovery that hippocampal lesions produced

anterograde amnesia in humans stimulated interest in

the exact role that this structure plays in the learning

process. To pursue this interest, researchers have developed

tasks that require relational learning, and laboratory

animals with hippocampal lesions show memory

deficits on such tasks, just as humans do.

Spatial Perception and Learning

As we saw, hippocampal lesions disrupt the ability to keep

track of and remember spatial locations. For example,

H. M. never learned to find his way home when his parents

moved after his surgery. Laboratory animals show

similar problems in navigation. Morris et al. (1982) developed

a task that other researchers have adopted as a standard

test of rodents’ spatial abilities. The task requires

rats to find a particular location in space solely by means

of visual cues external to the apparatus. The “maze” consists

of a circular pool, 1.3 meters in diameter, filled with

a mixture of water and something to increase the opacity

of the water, such as powdered milk. The water mixture

hides the location of a small platform, situated just

beneath the surface of the liquid. The experimenters put

the rats into the water and let them swim until they

encountered the hidden platform and climbed onto it.

They released the rats from a new position on each trial.

After a few trials, normal rats learned to swim directly to

the hidden platform from wherever they were released.

The Morris water maze requires relational learning;

to navigate around the maze, the animals get their bearings

from the relative locations of stimuli located outside

the maze—furniture, windows, doors, and so on. But the

0.7

0.8

0.9

1.0 Hippocampus

–1 0 1 2 3 4 5

0

0.1

0.2

0.3

0.4 Caudate nucleus

–1 0 1 2 3 4 5

Errors

Relative volume

of gray matter

Relative volume

of gray matter

**FIGURE 13.36** ■ **Spatial and Response Strategies .**

The figure shows the relation between volume of gray matter of the hippocampus (top)

and caudate nucleus (bottom) and errors made on test trials in a virtual maze that could

be performed only by using a response strategy. Increased density of the caudate nucleus

was associated with better performance, and increased density of the hippocampus was

associated with poorer performance.

(From Bohbot, V. D., Lerch, J., Thorndycraft, B., Iaria, G., and Zijdenbos, A. *Journal of Neuroscience,* 2007*, 27,*

10078–10083. Reprinted with permission.)

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maze can be used for nonrelational, stimulus-response

learning too. If the animals are always released at the same

place, they learn to head in a particular direction—say,

toward a particular landmark they can see above the wall

of the maze (Eichenbaum, Stewart, and Morris, 1990).

If rats with hippocampal lesions are always released

from the same place, they learn this nonrelational, stimulus-

response task about as well as normal rats do. However,

if they are released from a new position on each trial, they

swim in what appears to be an aimless fashion until they

finally encounter the platform. (See ***Figure 13.37.***)

Many different types of studies have confirmed the

importance of the hippocampus in spatial learning. For

example, Gagliardo, Ioalé, and Bingman (1999) found

that hippocampal lesions disrupted navigation in homing

pigeons. The lesions did not disrupt the birds’ ability

to use the position of the sun at a particular time of day

as a compass pointing toward their home roost. Instead,

the lesions disrupted their ability to keep track of where

they were when they got near the end of their flight—at

a time when the birds begin to use familiar landmarks to

determine where they are. In a review of the literature,

Sherry, Jacobs, and Gaulin (1992) reported that the hippocampal

formation of species of birds and rodents that

normally store seeds in hidden caches and later retrieve

them (and that have excellent memories for spatial locations)

is larger than that of animals without this ability.

Place Cells in the Hippocampal

Formation

One of the most intriguing discoveries about the hippocampal

formation was made by O’Keefe and

Dostrovsky (1971), who recorded the activity of individual

pyramidal cells in the hippocampus as an animal moved

around the environment. The experimenters found that

(a)

Variable start positions

(relational task)

Constant start position

(stimulus-response task)

(b)

Hidden

platform

Control

Lesion

Start

Finish

(d)

2 4 6 8 10 12

20

20

40

60

40

60

80

100

120

0

Mean latency (s)

Mean latency (s)

Variable start positions

(relational task)

Constant start position

(stimulus-response task)

Trials Trials

(c)

Lesion

Control

2–6 7–12 13–18

**FIGURE 13.37** ■ **The Morris Water Maze .**

(a) Environmental cues present in the room provide information that permits the animals to

orient themselves in space. (b) According to the task, start positions are variable or fixed.

Normally, rats are released from a different position on each trial. If they are released from

the same position every time, the rats can learn to find the hidden platform through stimulusresponse

learning. (c) The graphs show the performance of normal rats and rats with

hippocampal lesions using variable or fixed start positions. Hippocampal lesions impair

acquisition of the relational task. (d) Representative samples show the paths followed by

normal rats and rats with hippocampal lesions on the relational task (variable start positions).

(Adapted from Eichenbaum, H. *Nature Reviews: Neuroscience,* 2000, *1,* 41–50. Data from Eichenbaum et al., 1990.)

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some neurons fired at a high rate only when the rat was

in a particular location. Different neurons had different

*spatial receptive fields;* that is, they responded when the animals

were in different locations. A particular neuron

might fire twenty times per second when the animal was

in a particular location but only a few times per hour

when the animal was located elsewhere. For obvious reasons

these neurons were named **place cells.**

When a rat is placed in a symmetrical chamber,

where there are few cues to distinguish one part of the

apparatus from another, the animal must keep track of

its location from objects it sees (or hears) in the environment

outside the maze. Changes in these items

affect the firing of the rats’ place cells as well as their

navigational ability. When experimenters move the

stimuli as a group, maintaining their relative positions,

the animals simply reorient their responses accordingly.

However, when the experimenters interchange the

stimuli so that they are arranged in a new order, the animals’

performance (and the firing of their place cells)

is disrupted. (Imagine how disoriented you might be if

you entered a familiar room and found that the windows,

doors, and furniture were in new positions.)

The fact that neurons in the hippocampal formation

have spatial receptive fields does not mean that

each neuron encodes a particular location. Instead, this

information is undoubtedly represented by particular

*patterns* of activity in circuits of large numbers of neurons

within the hippocampal formation. In rodents

most hippocampal place cells are found in the dorsal

hippocampus, which corresponds to the posterior hippocampus

in humans (Best, White, and Minai, 2001).

Evidence indicates that firing of hippocampal place

cells appears to reflect the location where an animal

“thinks” it is. Skaggs and McNaughton (1998) constructed

an apparatus that contained two nearly identical chambers

connected by a corridor. Each day, rats were placed

in one of the chambers, and a cluster of electrodes in

the animals’ brains recorded the activity of hippocampal

place cells. Each rat was always placed in the same

chamber each day. Some of the place cells showed similar

patterns of activity in each of the chambers, and some

showed different patterns, which suggests that the hippocampus

“realized” that there were two different compartments

but also “recognized” the similarities between

them. Then, on the last day of the experiment, the

investigators placed the rats in the other chamber of the

apparatus. For example, if a rat was usually placed in

the north chamber, it was placed in the south chamber.

The firing pattern of the place cells in at least half of the

rats indicated that the hippocampus “thought” it was in

the usual chamber—the one to the north. However,

once the rat left the chamber and entered the corridor,

it saw that it had to turn to the left to get to the other

chamber and not to the right. The animal apparently

realized its mistake, because for the rest of that session

the neurons fired appropriately. They displayed the

“north” pattern in the north chamber and the “south”

pattern in the south chamber. (See ***Figure 13.38.***)

The hippocampus appears to receive its spatial information

from the parietal lobes by means of the entorhinal

cortex. Sato et al. (2006) found that neurons in the

medial parietal cortex of monkeys showed activity associated

with specific movements at specific locations as the

animals navigated a virtual environment with a joystick.

(Yes, monkeys, too, can learn to play computer games.)

When the investigators suppressed activity in the parietal

cortex by infusing muscimol, the animals became lost.

Quirk et al. (1992) found that neurons in the entorhinal

cortex have spatial receptive fields, although these fields

are not nearly as clear-cut as those of hippocampal

pyramidal cells. Damage to the entorhinal cortex disrupts

the spatial receptive fields of place cells in the hippocampus

and impairs the animals’ ability to navigate in spatial

tasks (Miller and Best, 1980).

**FIGURE 13.38** ■ **Apparatus Used by .**

**Skaggs and McNaughton (1998) .**

Place cells reflect the location where the animal “thinks” it is.

Because the rat was normally placed in the north chamber,

its hippocampal place cells responded as if it were there

when it was placed in the south chamber one day. However,

once it stuck its head into the corridor, it saw that the other

chamber was located to its right, so it “realized” that it had

just been in the south chamber. From then on, the pattern of

firing of the hippocampal place cells accurately reflected the

chamber in which the animal was located.

N

S

W E

**place cell** A neuron that becomes active when the animal is in a

particular location in the environment; most typically found in the

hippocampal formation.

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The activity of circuits of hippocampal place cells

provide information about more than space. Wood et al.

(2000) trained rats on a spatial alternation task in a Tmaze.

The task required the rats to enter the left and the

right arms on alternate trials; when they did so, they

received a piece of food in goal boxes located at the

ends of the arms of the T. Corridors connected the goal

boxes led back to the stem of the T-maze, where the

next trial began. (See ***Figure 13.39.***) Wood and her colleagues

recorded from field CA1 pyramidal cells and, as

expected, found that different cells fired when the rat

was in different parts of the maze. However, two-thirds

of the neurons fired differentially in the stem of the T

on left-turn and right-turn trials. In other words, the

cells not only encoded the rat’s location in the maze, but

also signaled whether the rat was going to turn right or

turn left after it got to the choice point. Thus, pyramidal

cells in CA1 encode both the current location and the

intended destination.

Role of the Hippocampal Formation

in Memory Consolidation

We have already seen evidence from functional-imaging

studies and the effects of brain damage in humans that

indicates that the hippocampal formation plays a critical

role in consolidation of relational memories. Studies with

laboratory animals support this conclusion. For example,

Bontempi et al. (1999) trained mice in a spatial learning

task. Five days later, they used a 2-DG imaging procedure

to measure regional brain activation while they tested the

animals’ memory for the task. The activity of the hippocampus

was elevated and was positively correlated with

the animal’s performance—the higher the activity, the

better the performance. At twenty-five days, hippocampal

activity was down by 15–20 percent, and the correlation

between activity and performance was gone. However, the

activity of several regions of the cerebral cortex was elevated

while the animals were being tested. The investigators

conclude that these findings support the hypothesis

that the hippocampus is involved in consolidation of spatial

memories for a limited time, and the result of this activity

is to help establish the memories in the cerebral cortex.

Maviel et al. (2004) trained mice in a Morris water

maze and tested later for their memory of the location

of the platform. Just before testing the animal’s performance,

the investigators temporarily deactivated specific

regions of the animals’ brains with intracerebral

infusions of lidocaine, a local anesthetic. If the hippocampus

was deactivated one day after training, the

mice showed no memory of the task. However, if the

hippocampus was deactivated thirty days after training,

their performance was normal. In contrast, inactivation

of several regions of the cerebral cortex impaired memory

retrieval thirty days after training, but not one day

after training. These findings indicate that the hippocampus

is required for newly learned spatial information

but not for information learned thirty days previously.

The findings also suggest that sometime during

these thirty days the cerebral cortex takes on a role in

retention of this information. (See ***Figure 13.40.***)

As we saw in Chapter 9, slow-wave sleep facilitates the

consolidation of declarative memories in human subjects,

while REM sleep facilitates the consolidation of nondeclarative

memories. One advantage of recording place

cells in the hippocampus while animals perform a spatial

task is that the investigators can detect different patterns

of activity in these cells that changes as the animals move

through different environments. Lee and Wilson (2002)

**FIGURE 13.40** ■ **A Schematic Description .**

**of the Experiment by Maviel et al. (2004) .**

Train

1 day or 30 days

Inject lidocaine

in hippocampus

then test: No memory

Inject lidocaine

in hippocampus

then test: Good memory

Train

1 day or 30 days

Inject lidocaine

in cortex

then test: Good memory

Inject lidocaine

in cortex

then test: No memory

**FIGURE 13.39** ■ **Apparatus Used by .**

**Wood et al. .**

The rats were trained to turn right and turn left at the end

of the stem of the T-maze on alternate trials. The firing

patterns of hippocampal place cells with spatial receptive

fields in the stem of the maze were different on trials during

which the animals turned left or right.

(Adapted from Wood, E. R., Dudchenko, P. A., Robitsek, R. J., and

Eichenbaum, H. *Neuron,* 2000, *27,* 623–633.)

Left-turn trial

Right-turn trial

Stem of

T-maze

Animal starts

here

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implanted an array of microelectrodes in field CA1 of rats

and were able to record from 24 to 57 different neurons

simultaneously in each animal. The rats ran through

straight or U-shaped tracks, at the ends of which they

found a piece of chocolate. The investigators recorded the

sequences of place cell activity in field CA1 as the animals

ran. They also recorded the activity of these cells while the

animals slept. They found that particular cells had particular

spatial receptive fields, so as the animals ran through

the tracks, particular sequences of cell firing were seen.

Recordings made after training showed the same patterns

of activity while the animals engaged in slow-wave sleep.

Presumably, these patterns indicate a replay of the animals’

behavior as they moved through their environment

and obtained the food, and the patterns facilitate consolidation

of the memories of these episodes.

Reconsolidation of Memories

What happens to memories of events as time goes on?

Clearly, if we learn something new about a particular

subject, our memories pertaining to that subject must

somehow be modified. For example, as I mentioned earlier

in this chapter, if a friend gets a new hairstyle or

replaces glasses with contact lenses, our visual memory

of that person will change accordingly. And if you learn

more about something—for example, the layout of a

previously unfamiliar neighborhood—you will acquire a

larger and larger number of interconnected memories.

These examples indicate that memories can be altered

or connected to newer memories. In recent years,

researchers have been investigating a phenomenon

known as **reconsolidation,** which appears to involve

modification of long-term memories.

As we will see in Chapter 16, one of the side effects

of a procedure known as electroconvulsive therapy is a

period of retrograde amnesia. The procedure, used to

treat cases of severe depression, involves the application

of electricity through electrodes placed on a person’s

scalp. The current excites so many neurons in the brain

that it produces a seizure. Presumably, the seizure erases

short-term memories present at the time and thus prevents

consolidation of these memories.

Misanin, Miller, and Lewis (1968) found that longterm

memories, which are normally not affected by

seizures, were vulnerable to disruption by electroconvulsive

shock (ECS) if a reminder of the original learning

experience was first presented. The investigators found

that ECS given right after a learning experience prevented

consolidation, but ECS given a day later did not.

Apparently, the seizure given right after training disrupted

the brain activity initiated by the training session and

consequently interfered with consolidation. The seizure

given the next day had no effect, because the memory

had already been consolidated. However, if animals

were given a “reminder” stimulus one day after training,

which presumably reactivated the memory, an ECS

treatment administered immediately afterward caused

amnesia for the task when the animals were tested the

following day. Reactivation of the memory made it susceptible

to disruption. (See ***Figure 13.41.***)

A study by Ben Mamou, Gamache, and Nader (2006)

found that the process of reconsolidation requires longterm

potentiation. The investigators found that injection

of *anisomycin,* a drug that prevents protein synthesis

and thus interferes with memory consolidation, would

disrupt memory of a previously learned avoidance task

only if a reminder stimulus was presented. However, if

an injection of an NMDA receptor antagonist was first

infused into the amygdala (the region involved in learning

this task), anisomycin had no effect on memory even

if a reminder stimulus was presented. These results indicate

that when synaptic plasticity is prevented, reconsolidation

cannot occur. Thus, reconsolidation requires

long-term potentiation.

The study by Misanin, Mamon, and their colleagues

involved stimulus-response learning. More recent studies

have found that long-term, well-consolidated relational

memories are also susceptible to disruption. Presumably,

the process of reconsolidation, which involves neural

events similar to those responsible for the original consolidation,

makes it possible for established memories to be

altered or attached to new information (Nader, 2003).

(Remember when I mentioned that seeing your friend

with a new hairstyle would alter your visual memory of

that person?) Events that interfere with consolidation

**FIGURE 13.41** ■ **A Schematic Description .**

**of the Experiment by Misanin, Miller, and .**

**Lewis (1968) .**

1 day

1 day

1 day 1 day

1 day

ECS

(no delay)

ECS

(no delay)

Train

Train

Train

Test: No memory

Test: No memory

ECS Test: Good memory

Present

CS

**reconsolidation** A process of consolidation of a memory that

occurs subsequent to the original consolidation that can be

triggered by a reminder of the original stimulus; thought to provide

the means for modifying existing memories.

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also interfere with reconsolidation and can even erase

memories or at least make them inaccessible. For example,

Debiec, LeDoux, and Nader (2002) trained rats on a

relational fear-conditioning task that required participation

of the hippocampus. If anisomycin was infused into

the hippocampus immediately after training, consolidation

did not occur. If the drug was infused 45 days later,

no effect was seen: The memory had already been consolidated.

However, if the memory was reactivated 45 days

later by presenting the CS that had been part of the original

learning session and the drug was then injected into

the hippocampus, the animals showed amnesia for the

training when they were tested later. (See ***Figure 13.42.***)

Role of Long-Term Potentiation

in Memory

Earlier in this chapter we saw how synaptic connections

could be quickly modified in the hippocampal formation,

leading to long-term potentiation or long-term

depression. How are these changes in synaptic strength

related to the role the hippocampus plays in learning?

As you just learned, place cells in the hippocampal

formation become active when the animal is present in

particular locations. The sensory information reaches

the dentate gyrus from the entorhinal cortex. Does

this increased activity cause changes in the excitability

of neurons in the hippocampal formation? The answer

is clearly “yes.” For example, Mitsuno et al. (1994) found

that as rats learned a maze, the strength of the population

EPSP in field CA3 increased. Thus, when animals learn

tasks that involve the hippocampal formation, the

experience appears to induce the same types of changes

that are produced by long-term potentiation.

More recently, researchers have developed targeted

mutations of the gene responsible for the production

of NMDA receptors, which, as we saw earlier, are

responsible for long-term potentiation in several parts

of the hippocampal formation. Two studies from the

same laboratory (McHugh et al., 1996; Tsien, Huerta,

and Tonegawa, 1996) produced a targeted mutation of

the NMDA receptor gene that affected only the CA1

pyramidal cells. NMDA receptors in these neurons

failed to develop; in all other parts of the brain these

receptors were normal. Figure 13.43. shows photomicrographs

of slices through the hippocampus of a normal

mouse and a knockout mouse, showing the presence

of the messenger RNA for the NMDA receptor,

revealed by in situ hybridization. As you can see, the

NMDA receptor is missing in the CA1 field of the

mouse with the targeted mutation. (See ***Figure 13.43.***)

As you might expect, the experimenters found that

the lack of NMDA receptors prevented the establishment

of long-term potentiation in field CA1 in the mice

with the targeted mutation. And although the pyramidal

cells of CA1 did show spatial receptive fields, these fields

were larger and less focused than those shown by cells in

normal animals. In addition, the knockout mice learned

a Morris water maze much more slowly than did mice

whose CA1 neurons contained NMDA receptors.

In summary, experimental evidence indicates that

the participation of the hippocampal formation in

learning involves long-term potentiation.

Role of Hippocampal Neurogenesis

in Consolidation

As we saw in Chapter 3, new neurons can be produced in

the hippocampus of the adult brain. Stem cells located

in the subgranular zone of the hippocampus divide and

give rise to granule cells, which migrate into the dentate

gyrus and extend axons along the mossy fiber tract. The

new neurons form connections with other neurons in

**FIGURE 13.43** ■ **Absence of NMDA .**

**Receptors in Field CA1 .**

Photomicrographs of sections through the hippocampus

show in situ hybridization of messenger RNA responsible

for the production of NMDA receptors. (a) Normal mouse.

(b) Mouse with the targeted mutation (CA1 knockout). This

photomicrograph shows the effects of a targeted mutation

(knockout) of the NMDA receptor gene that is expressed only

in field CA1 of the hippocampus. Ctx = neocortex, CA1 =

hippocampal field CA1, DG = dentate gyrus.

(From Tsien, J. Z., Huerta, P. T., and Tonegawa, S. *Cell,* 1996, *87,*

1327–1338. Reprinted by permission.)

Control CA1-KO

(a) (b)

**FIGURE 13.42** ■ **A Schematic Description .**

**of the Experiment by Debiec et al. (2002) .**

45 days

45 days

1 day

90 sec

CS

Inject

drug

Inject

drug

Test: No memory

Test: Good memory

Train

Train

1 day

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**InterimSummary**

**Relational Learning**

Brain damage can produce anterograde amnesia, which consists

of the inability to remember events that happen after

the damage occurs, even though short-term memory (such as

that needed to carry on a conversation) is largely intact. The

patients also have a retrograde amnesia of several years’

duration but can remember information from the distant

past. Anterograde amnesia can be caused by chronic alcoholism

(Korsakoff’s syndrome), which primarily damages the

mammillary bodies, or it can be produced by bilateral damage

to the medial temporal lobes.

The first explanation for anterograde amnesia was that

the ability of the brain to consolidate short-term memories

into long-term memories was damaged. However, ordinary

perceptual learning, stimulus-response learning, and motor

learning do not appear to be impaired; people can learn to

recognize new stimuli, they are capable of instrumental and

classical conditioning, and they can acquire motor memories.

But they are not capable of *declarative learning—*of

describing events that happen to them. The amnesia has also

been called a deficit in explicit memory. An even more

descriptive term—one that applies to laboratory animals as

well as to humans—is *relational learning.*

Although other structures may be involved, researchers are

now confident that the primary cause of anterograde amnesia

is damage to the hippocampal formation or to its inputs and

outputs. Temporary anoxia damages field CA1 because of the

high concentration of NMDA receptors there and produces

anterograde amnesia. The entorhinal cortex receives informathe

dentate gyrus and with neurons in field CA3

(Kempermann, Wiskott, and Gage, 2004).

Gould et al. (1999) trained rats on two versions of

the Morris water maze: one requiring relational learning

and one requiring only stimulus-response learning.

Training on the relational task, which involves the hippocampus,

doubled the number of newborn neurons

in the dentate gyrus. Training on the stimulus-response

task, which does not involve the hippocampus, had no

effect on neurogenesis. Evidence also suggests that new

neurons in the dentate gyrus participate in learning.

Jessberger and Kempermann (2003) trained mice on a

relational learning task in a Morris water maze and

found an increase in fos protein in newly formed dentate

gyrus neurons, which indicates that the neurons

had been activated by the experience.

Schmidt-Hieber, Jonas, and Bischofberger (2004)

found that it was easier to establish associative long-term

potentiation in newly formed neurons than in older

neurons. They suggest that neurogenesis could be a

mechanism that facilitates synaptic plasticity by providing

a continuously available pool of neurons to participate

in the formation of new memories.

Kempermann, Wiskott, and Gage (2004) note that

although learning experiences increase the number

of new neurons in the hippocampus, maturation of

these neurons and the establishment of their connections

with other neurons take a considerable amount

of time; thus, enhanced neurogenesis is of benefit to

the animal only on a long-term basis. We do not yet

understand the exact role of neurogenesis in learning

and adaptation, nor can we explain why neurogenesis

takes place in only two regions, the olfactory bulb and

the hippocampus. If neurogenesis is useful in these

places, why does it not occur elsewhere in the brain?

tion from all regions of the association cortex, directly and

through its connections with the perirhinal and parahippocampal

cortex that surrounds it. The outputs of the hippocampal

formation are relayed through these same regions.

The hippocampal formation receives information from

other regions of the brain, processes this information, and

then, through its *efferent* connections with these regions,

modifies the memories that are being consolidated there,

linking them together in ways that will permit us to remember

the relationships among the elements of the memories.

If damage is limited to the hippocampus, the anterograde

amnesia this destruction causes will be accompanied

by a retrograde amnesia of a few years. Damage that

includes the limbic cortex of the medial temporal lobe as

well as the hippocampal formation produces a much longer

retrograde amnesia, but patients are able to recall episodic

information from their childhood.

Damage to the neocortex of the anterolateral temporal

lobes causes semantic dementia, loss of memories of factual

information. These symptoms are mimicked by transcranial

magnetic stimulation of this region. If the damage is limited

to this region, people do not sustain an anterograde amnesia

and retain the ability to recall episodic information.

The hippocampal formation—especially the right posterior

hippocampus—is involved in spatial memory.

Functional-imaging studies have shown that performance of

spatial tasks increases activity in this region.

Studies with laboratory animals indicate that damage to

the hippocampal formation disrupts the ability to learn spatial

relations. For example, rats with hippocampal damage

cannot learn the Morris water maze unless they are always

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released from the same place in the maze, which turns the

task into one of stimulus-response learning. The hippocampal

formation contains place cells—neurons that respond

when the animal is in a particular location, which implies

that the hippocampus contains neural networks that keep

track of the relationships among stimuli in the environment

that define the animal’s location. Neurons in the hippocampal

formation reflect where an animal “thinks” it is.

Topographical information reaches field CA1 of hippocampus

from the parietal lobe by means of the entorhinal cortex.

Place cells encode more than space; they can include information

about the response that the animal will perform next.

Research has shown that the hippocampal formation plays

a role in memory consolidation. A 2-DG imaging study found

that the hippocampal activity correlates with animals’ ability to

remember a spatial learning task a few days after the original

learning but that the correlation disappears after a few weeks.

Similarly, deactivation of the dorsal hippocampus prevents consolidation

if it occurs one day after the animal learns a Morris

water maze task but has no effect if it occurs thirty days later.

In contrast, deactivation of regions of the cerebral cortex thirty

days after training disrupt performance if it occurs thirty days

after training but has no effect if it occurs one day after training.

Slow-wave sleep facilitates the consolidation of declarative

memories, and REM sleep facilitates the consolidation of nondeclarative

memories. During slow-wave sleep, place cells in

field CA1 of rats replay the sequence of activity that they

showed while navigating in an environment in the laboratory.

Memories can be altered or connected to newer

memories—a process known as reconsolidation. When a

long-term memory is reactivated by stimuli that provide a

“reminder” of the original experience, the memories become

susceptible to events that interfere with consolidation, such

as electroconvulsive shock treatment, interference with longterm

potentiation, or the administration of a drug that

inhibits protein synthesis.

Learning involves long-term potentiation. When rats are

trained in a maze, synaptic connections in the hippocampus

are strengthened. A targeted mutation against the NMDA

receptor gene that affects only field CA1 disrupts long-term

potentiation and the ability to learn the Morris water maze.

The dentate gyrus is one of the two places in the brain

where adult stem cells can divide and give rise to new neurons.

These neurons establish connections with neurons in field CA3

and appear to participate in learning. Their ability to undergo

long-term potentiation more easily than older neurons suggests

that they facilitate the formation of new memories.

**Thought Question**

Although we can live only in the present, our memories are

an important aspect of our identities. What do you think it

would be like to have a memory deficit like H. M.’s? Imagine

having no recollection of over thirty years of experiences.

Imagine being surprised every time you see yourself in the

mirror and discover someone who is more than thirty years

older than you believe yourself to be.

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