10 Cholinergic Modulation of Hippocampal-Region Function

Previous chapters have discussed various aspects of the interaction between the hippocampal region, cortex, and cerebellum. An emerging theme is that the hippocampal region does not operate in isolation. Areas such as cortex provide input to the hippocampal region and are the eventual targets of its output.

Other brain structures modulate hippocampal-region processing. These other structures provide chemical messengers—**neurotransmitters** and **neuromodulators**—that affect how hippocampal-region neurons behave. One of the principal neuromodulatory systems arises in the **medial septum,** a small group of cells that project to the hippocampus. Some of these cells are **cholinergic** neurons, meaning that they produce the neurotransmitter **acetylcholine** (abbreviated **ACh**).

This cholinergic input is critical for normal hippocampal function. When the septohippocampal cholinergic pathway is disrupted through damage to the medial septum or with drugs that affect ACh efficacy, hippocampal-region function is disrupted. In many cases, *hippocampal-region disruption has qualitatively different effects on learning and memory behavior than direct hippocampal-region damage.*

This chapter begins by first providing a brief review of neurotransmission and neuromodulation, with particular attention to acetylcholine and how it affects memory. Next, the chapter discusses computational models suggesting that acetylcholine provided from medial septum to hippocampus is integral in mediating hippocampal function and a model that addresses the effects of changes in acetylcholine levels on learning and memory. Finally, the chapter discusses how these models relate to other theories of septohippocampal modulation and how they may apply to research with various patient populations.

10.1 ACETYLCHOLINE AS A NEUROMODULATOR

Back in chapter 3, we discussed the basic anatomy of neurons that receive inputs through their dendrites and send output via axons to other neurons (figure 10.1A). To review, the small gap between neurons is called a **synapse;** when a sending (or **presynaptic**) neuron becomes sufficiently activated, it releases chemicals called **neurotransmitters** into the synapse. The receiving (or **postsynaptic**) neuron contains **receptors,** each keyed to respond to a particular kind of neurotransmitter. *Different neurotransmitters have different effects on the postsynaptic neuron, and the postsynaptic neuron's response depends on the sum of all these effects.* Any neurotransmitter that does not attach to a receptor is quickly cleaned out of the synapse; lingering

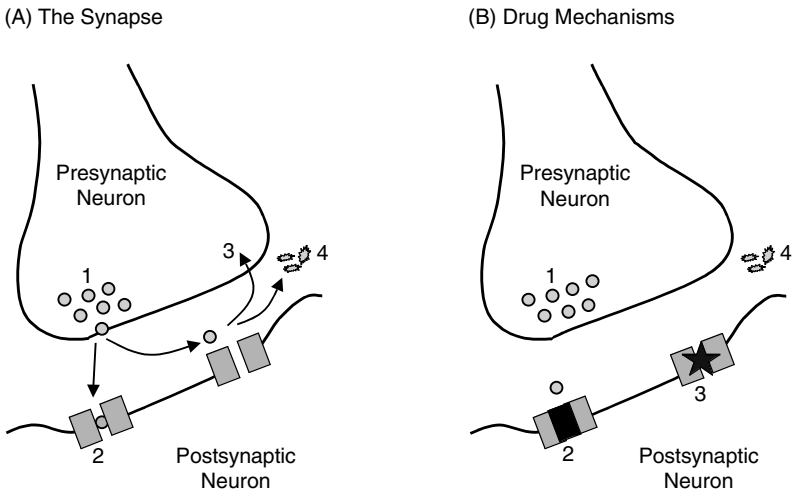

Figure 10.1 (A) Schematic of synaptic transmission. A sending (presynaptic) neuron releases chemicals called neurotransmitters (1) from its axon into a small gap (synapse). The receiving (postsynaptic) cell contains receptors (2), which are activated by specific neurotransmitters. Any remaining neurotransmitter is cleaned out of the synapse—either taken back into the presynaptic cell and recycled (3) or broken down into chemical components (4). (B) Drugs work by altering synaptic transmission. Presynaptically, drugs may alter the rates at which transmitters are produced or released (1). Postsynaptically, drugs may block receptors (2), preventing neurotransmitters from reaching their destination and interfering with transmission. Drugs may mimic neurotransmitters (3), even activating receptors more efficiently than the neurotransmitter itself. Other drugs act by affecting the rate at which neurotransmitter is removed from the synapse (4); neurotransmitter that remains in the synapse longer has more chance of eventually activating a receptor. Thus, a drug that decreases synaptic cleanup facilitates transmission.

neurotransmitter molecules are either reabsorbed by the presynaptic neuron and recycled for future use or broken down into smaller chemical components.

Drugs can affect neurotransmission by altering any step of this process (figure 10.1B); **agonists** facilitate transmission while **antagonists** impede transmission. Some drugs act presynaptically, altering the rate at which neurotransmitter molecules are produced or released. For example, botulinum toxin, the substance that causes botulism, is a cholinergic antagonist that prevents the release of ACh. The venom of the black widow spider is a cholinergic agonist, which causes an equally lethal overrelease of ACh—flooding the system. Alternatively, some drugs act postsynaptically. Nicotine is a cholinergic agonist that can activate one kind of cholinergic receptor, "tricking" the postsynaptic cell into thinking that it has received ACh. Drugs can also block receptors, preventing neurotransmitters from attaching to the postsynaptic cell. Scopolamine—once used as an analgesic during childbirth and currently marketed as a motion-sickness remedy—is a cholinergic antagonist that blocks cholinergic transmission in this way. *Finally, other drugs affect the cleanup process:* If the rate of molecular breakdown or recycling is reduced, neurotransmitters remain in the synapse longer and have more of a chance to attach to receptors. The drugs tacrine (brand name Cognex) and donepezil (trade name Aricept), which are currently marketed for treating Alzheimer's disease, work by slowing down the processes that cleans up unused ACh from the synapses, thereby allowing the existing ACh molecules to linger, increasing the chances that they will contact a postsynaptic receptor.

Neuromodulation

Neurotransmitters carry specific neural "messages" from one neuron to another. An excitatory neurotransmitter increases the probability that the postsynaptic neuron will become active (passing the message on), and an inhibitory neurotransmitter decreases this probability. A different means of neuronal communication is via **neuromodulators.** *Whereas neurotransmitters carry the messages between neurons, neuromodulators affect how those messages are processed.* For example, a neuromodulator might increase the overall responsiveness of a postsynaptic neuron to other, incoming neurotransmitter messages.

A simple metaphor for these processes is radio transmission. The neurotransmitters carry the signal being broadcast—the words or music. Neuromodulators act like the volume control on the radio receiver. The volume

control adjusts how the message is transmitted without changing the content of that message.

Neuromodulators activate receptors according to the same basic principles of neurotransmission shown in figure 10.1. In fact, a single chemical substance can sometimes act as either a neurotransmitter or a neuromodulator. Acetylcholine has this dual role: Outside the brain, ACh acts as a neurotransmitter, carrying specific commands from the spinal cord to muscles throughout the body. Inside the brain, ACh acts like a neuromodulator, broadcasting general information across wide areas.

Acetylcholine (ACh) and Memory Function

In this chapter, we focus on the neuromodulatory effects of acetylcholine; some of the basic principles are similar for other neuromodulators.[1] Neurons that contain acetylcholine (cholinergic neurons) exist in several areas of the brain, including the **basal forebrain,** shown in figure 10.2. Within the basal

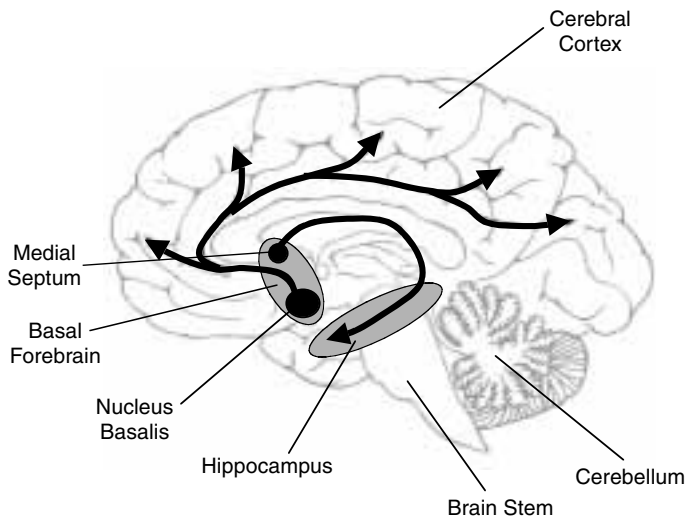

Figure 10.2 Schematic of some important cholinergic projections in the human brain. The basal forebrain is a small region that includes the medial septum, nucleus basalis, and other cell groups. The medial septum sends a cholinergic projection to hippocampus, while the nucleus basalis sends cholinergic projections throughout cortex. Other basal forebrain areas project to other brain structures. Some structures in the brain stem also send cholinergic projections to subcortical areas and out of the brain to neurons in the spinal cord that innervate muscles and control movements.

forebrain, one group of cells, called the **nucleus basalis,** projects ACh throughout the cortex, while another cell group, the **medial septum,** is a primary source of cholinergic projections to the hippocampus.* These latter pathways are often termed the **septohippocampal projection.**

Acetylcholine has a number of neuromodulatory effects.[2] These effects are varied, and not all their implications are yet clear. For example, application of acetylcholine itself (or cholinergic agonists that enhance the efficacy of ACh) can lead to a general increase in activity in pyramidal neurons. At the same time, ACh increases the spontaneous firing rates of inhibitory cells while decreasing the responsiveness of these cells to synaptic transmission. In addition, ACh appears to facilitate synaptic plasticity and hence to facilitate learning.

One of the reasons that acetylcholine has received so much attention is that disruption of the cholinergic system can have a devastating effect on memory. Disrupting the septohippocampal projection disrupts hippocampal function[3] and can cause memory impairments.[4] Drugs that are cholinergic antagonists, blocking the efficacy of ACh receptors in the brain, can also cause memory disruption.[5]

One well-known cholinergic antagonist is **scopolamine.**[6] Scopolamine can temporarily disable cholinergic pathways, including those from medial septum to hippocampus. The behavioral effect is a form of temporary amnesia. For example, normal human volunteers may be given a dose of scopolamine and then presented with information to study. Later, when the drug has cleared out of their systems, the volunteers have little or no memory of the information—or indeed of the study episode.[7] In effect, scopolamine induces temporary anterograde amnesia in subjects with no hippocampal-region damage.

However, the effects of cholinergic disruption are not identical to the effects of hippocampal lesion.[8] One example is classical conditioning of motor reflexes. Direct damage to the hippocampal region does not affect acquisition of a conditioned eyeblink response in animals or humans (figure 10.3A).[9] However, scopolamine does disrupt eyeblink conditioning (figure 10.3B).[10] Removal of the medial septum—which permanently disrupts the septohippocampal cholinergic projections—has an even more devastating effect on acquisition of eyeblink conditioning (figure 10.3C).[11] Thus, in classical

*In humans, the primary cholinergic input from basal forebrain to hippocampus comes from a nearby structure, called the diagonal band of Broca. The diagonal band and medial septum are so interrelated that they are often conceived as a single, compound structure (i.e., the medial septum/diagonal band complex).

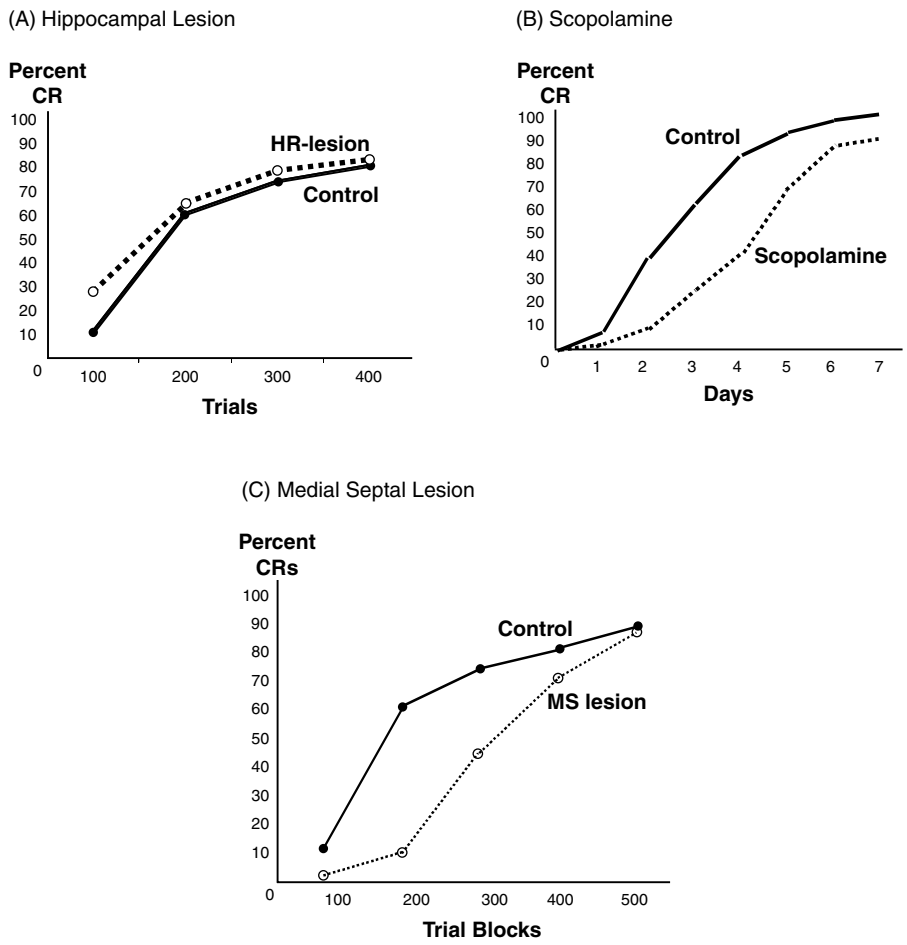

Figure 10.3 (A) Direct lesion to the hippocampus or hippocampal region does not impair acquisition of a conditioned eyeblink response in rabbits (Allen, Chelius, & Gluck, 1998). (B) Disruption of hippocampal function by administration of a cholinergic antagonist (scopolamine) to disrupt septohippocampal cholinergic projections does slow eyeblink conditioning, although subjects eventually reach normal performance levels (Solomon et al., 1983). (C) Lesion of the medial septum also disrupts conditioning (Ermita et al., 1999).

eyeblink conditioning, disrupting the hippocampus is actually worse than removing it altogether. In the next section, we will present computational models that address some of these behavioral data and provide an interpretation of these seemingly paradoxical findings.

10.2 COMPUTATIONAL MODELS

Acetylcholine in the Hippocampal Autoassociator

Many computational models, including some discussed in chapter 5, assume that hippocampal field CA3 functions as an autoassociator. That is, a pattern of input activations is stored in the CA3 network by strengthening connections between pairs of nodes that are simultaneously active, as shown in figures 10.4A and 10.4B. Later, when a partial or distorted version of a stored pattern is presented as input (figure 10.4C), this activates the corresponding subset of the nodes in the stored pattern, and from these nodes, activity will spread to the remaining nodes, retrieving the rest of the pattern (figure 10.4D).

However, there is a conceptual problem with this kind of autoassociator network, one that is often glossed over in the literature. Suppose that a pattern has previously been stored in the network that activates nodes A, B, C, and D and the connections between these nodes are strengthened as illustrated in figure 10.5A. Now a second pattern is presented for storage; this pattern activates

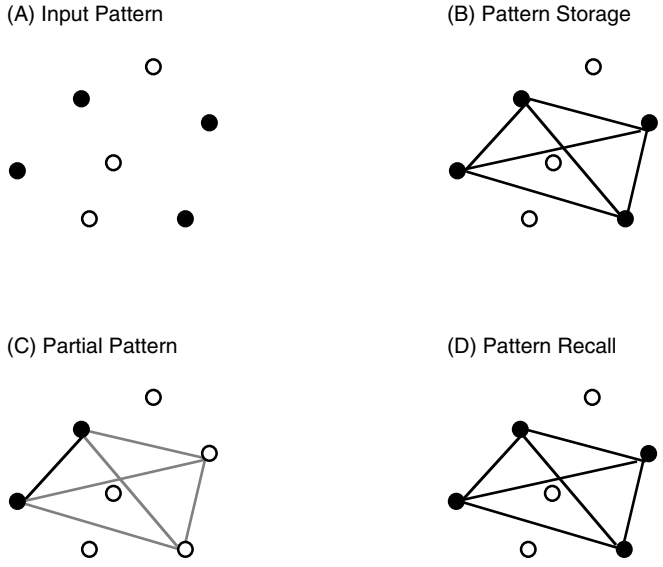

Figure 10.4 In the basic autoassociator, patterns are stored by strengthening associations between coactive nodes. (A) A pattern is presented that activates a subset of nodes (dark circles); (B) the pattern is stored by strengthening associations between these coactive nodes (shown as lines connecting active nodes). (C) Later, when a partial version of the pattern is presented (dark circles), activation spreads along these connections to recall the original stored pattern (D).

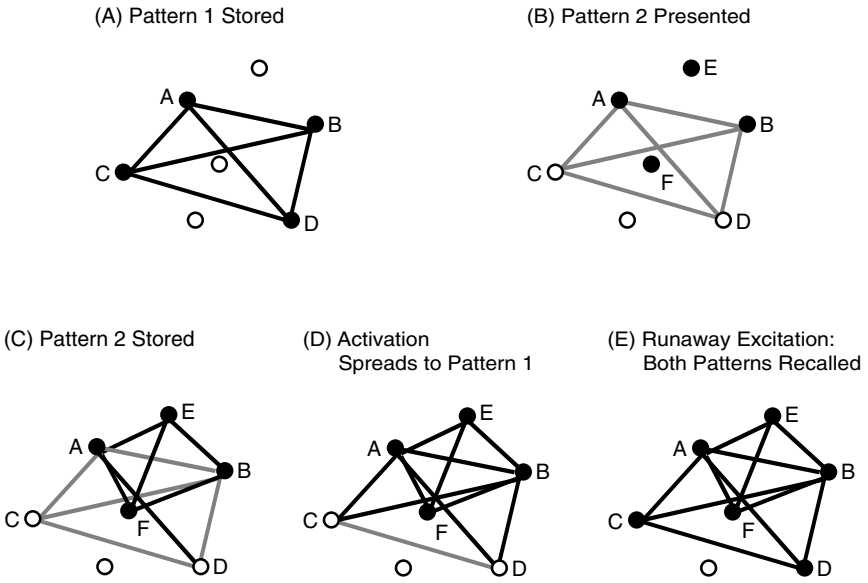

Figure 10.5 Runaway excitation in an autoassociative network. (A) Suppose one pattern (which activates nodes A, B, C, and D) has been stored by strengthening connections between coactive nodes (heavy lines). (B) Now a second pattern (which activates nodes A, B, E, and F) is to be stored. (C) First, associations between coactive nodes are strengthened. (D) However, the activation of nodes A and B will also spread along previously strengthened connections to activate nodes C and D. (E) Once C and D are activated, connections will be strengthened between them and other coactive nodes. The result is that a pattern is stored that is an amalgam of the two original patterns. In computational models, runaway excitation is often prevented by assuming that recall and storage are separate phases. Thus, the spreading activation shown in D does not occur during a storage phase. However, most models do not consider how such a restriction might be implemented physiologically.

nodes A, B, E, and F, partially overlapping with the first stored pattern (figure 10.5B). Connections between coactive nodes will be strengthened, storing the second pattern (figure 10.5C), *but* at the same time, activity will spread along connections that were previously strengthened, activating nodes C and D (figure 10.5D). When nodes C and D become active, connections between those nodes and other coactive nodes will be strengthened (figure 10.5E), creating a new pattern that is an amalgam of the two stored patterns. This process is known as **runaway excitation:** Presentation of one pattern for storage will activate all other patterns that share common elements. If storage occurs under such conditions, the result will be **runaway synaptic modification** as weights between all coactive nodes are strengthened.

To avoid this problem, computational modelers working with autoassociative networks have usually assumed that there are discrete storage and recall phases of the network's operation; during the storage phase, plasticity takes place between coactive cells, but this activity is not allowed to spread to other cells within the network. In other words, using the example of figure 10.5, the chain of events would proceed from figure 10.5A through 10.5C , but the spread of activation along previously strengthened connections (figure 10.5D) would be prevented.

This solution works well enough in a computational model because the human programmer can decide which state the network is in (recall or storage) and therefore which connections should be active or inactive at any given point. But in the brain there is no programmer who can decide when storage should take place and helpfully disable inopportune pathways. If a biological network indeed functions as an autoassociator, there must be a biological mechanism that can guide storage, allowing synaptic plasticity along new pathways (figure 10.5C) while preventing synaptic transmission along old pathways (figure 10.5D).

Michael Hasselmo and his colleagues have suggested a possible mechanism for these two processes to work together within the same circuit.[12] Hasselmo's idea is based on a curious feature of acetylcholine: It has different effects on different portions of a neuron. In general, ACh suppresses synaptic transmission; that is, given a fixed amount of excitatory neurotransmitter released from the presynaptic neuron, ACh makes the postsynaptic neuron less likely to become active in response to that input. But the specific amount of suppression varies for different kinds of inputs.

As is shown in figure 10.6, pyramidal cell bodies lie in one layer (called the *stratum pyramidale,* or pyramidal layer) of hippocampal field CA3, but their dendrites and axons extend into other layers. The inputs making synapses on the dendrites are largely segregated by layer. Inputs from the entorhinal cortex tend to synapse far from the cell bodies, in the *stratum lacunosum-moleculare*. Inputs from other CA3 neurons tend to synapse near the cell bodies, in the *stratum radiatum.* In other words, **extrinsic inputs,** arising outside the hippocampus, synapse in one layer, while **intrinsic inputs,** from inside the hippocampus, synapse in another layer.

When a cholinergic agonist is applied to CA3, its effects on suppressing synaptic transmission are much more pronounced in stratum radiatum than in stratum lacunosum-moleculare.[13] *That is, ACh appears to suppress intrinsic inputs more than extrinsic inputs* (figure 10.7).

A similar pattern of connectivity is seen in hippocampal field CA1:[14] ACh suppresses intrinsic inputs (from elsewhere in the hippocampus) more than

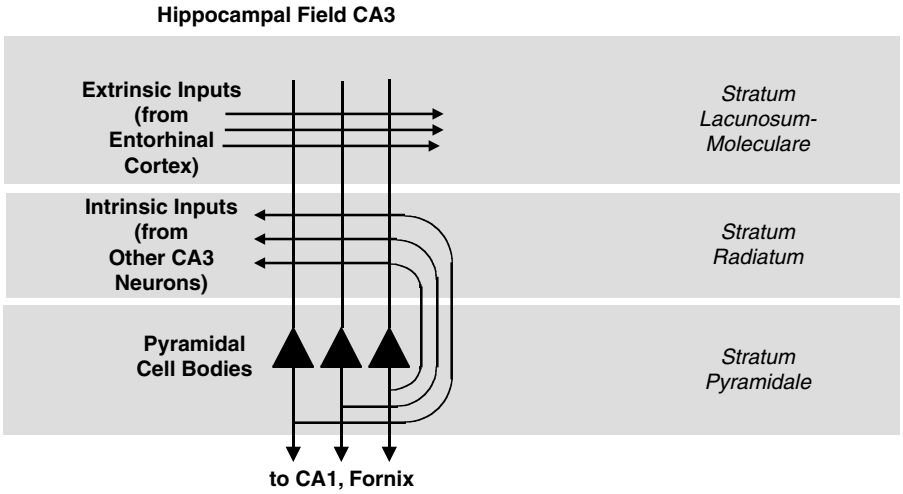

Figure 10.6 Schematic representation of hippocampal field CA3. CA3 is segregated into several layers, each defined by what types of cell bodies and inputs it contains. Pyramidal cells are located in the *stratum pyramidale,* and their dendritic processes reach up into *stratum radiatum* and *stratum lacunosum-moleculare.* The inputs that make synapses in *stratum lacunosum-moleculare* are largely extrinsic inputs from entorhinal cortex, whereas *stratum radiatum* contains intrinsic inputs, synapses from other CA3 cells. Acetylcholine acts selectively to suppress the intrinsic inputs more than the extrinsic inputs.

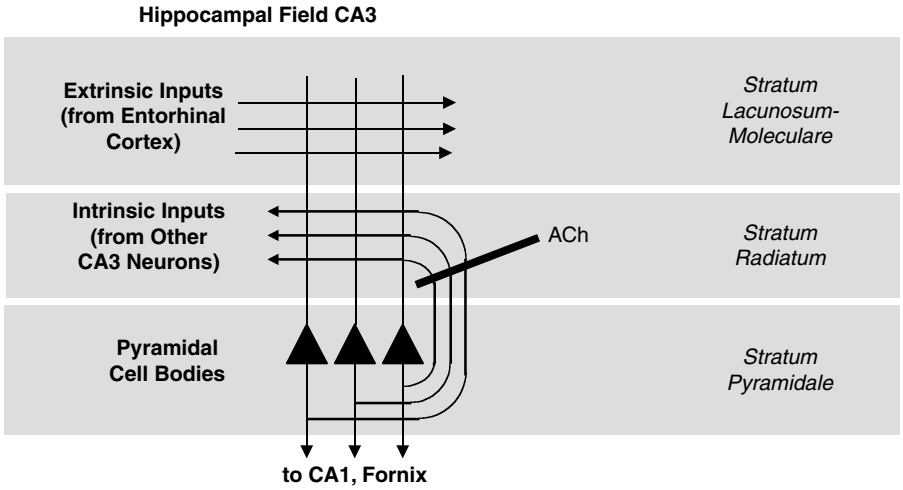

Figure 10.7 Hasselmo and colleagues have demonstrated that acetylcholine (ACh) has a suppressive effect on neuronal transmission that is more pronounced in *stratum radiatum* than in *stratum lacunosum-moleculare* in CA3. This means that ACh selectively suppresses intrinsic inputs (from other CA3 neurons) more than extrinsic inputs (from outside the hippocampus).

extrinsic inputs (from the entorhinal cortex). Other studies have demonstrated similar selectivity of cholinergic effects in dentate gyrus and cortex.[15] Thus, a basic principle of cholinergic function may be that ACh and cholinergic agonists exert a strong suppressive effect on *intrinsic* inputs but have little effect on *extrinsic* inputs.

Hasselmo has suggested how this property of ACh can be used to guide an associative network between storage and recall processing whereby *high levels of ACh suppresses intrinsic inputs, allowing storage, and low levels of ACh allow activity among intrinsic inputs, allowing recall.* This means that when cholinergic input is present, the hippocampus can store new patterns; when this ACh is absent, the hippocampus can retrieve patterns that were previously stored.

Figure 10.8 shows an example. A pattern is presented for storage to the CA3 network (figure 10.8A). The input activates a subset of the entorhinal afferents (e.g., a and b), which in turn activate a subset of CA3 pyramidal neurons (e.g., A and B). Acetylcholine suppresses activation along the recurrent collaterals (figure 10.8B) so that no additional CA3 pyramidal neurons are activated. However, enough activation passes to allow strengthening of connections between coactive CA3 neurons. At this point, the pattern AB is stored. Now suppose that a subset of the entorhinal inputs are presented—such as just afferent a (figure 10.8C). Node A is activated, and in the absence of acetylcholine, activation spreads along recurrent collaterals (figure 10.8D). The previously weighted connection between A and B allows node B to become active: The stored pattern is recalled. Finally, suppose another pattern is presented for storage. Entorhinal afferents b and c activate CA3 neurons B and C (figure 10.8E). In the presence of acetylcholine, activation is not allowed to spread along the previous connection from B to A, and so A does not become active. Thus, only the current pattern is stored; pieces of previous patterns do not intrude.

The basic assumption underlying the model in figure 10.8 is that acetylcholine should project from medial septum to hippocampus when novel input is to be stored but not while familiar input is being recalled. Important evidence of this effect has recently emerged. These data were obtained through microdialysis, an elegant technique for measuring local changes in neurotransmitter levels, and showed that the amount of acetylcholine in the ventral hippocampus increases during CS-US learning and decreases after the CR is well learned.[16] This is consistent with Hasselmo's assumption that acetylcholine levels should be high during learning and low thereafter.

Behavioral Predictions. Hasselmo's model expects that new information is stored in the presence of acetylcholine. Therefore, drugs that reduce brain

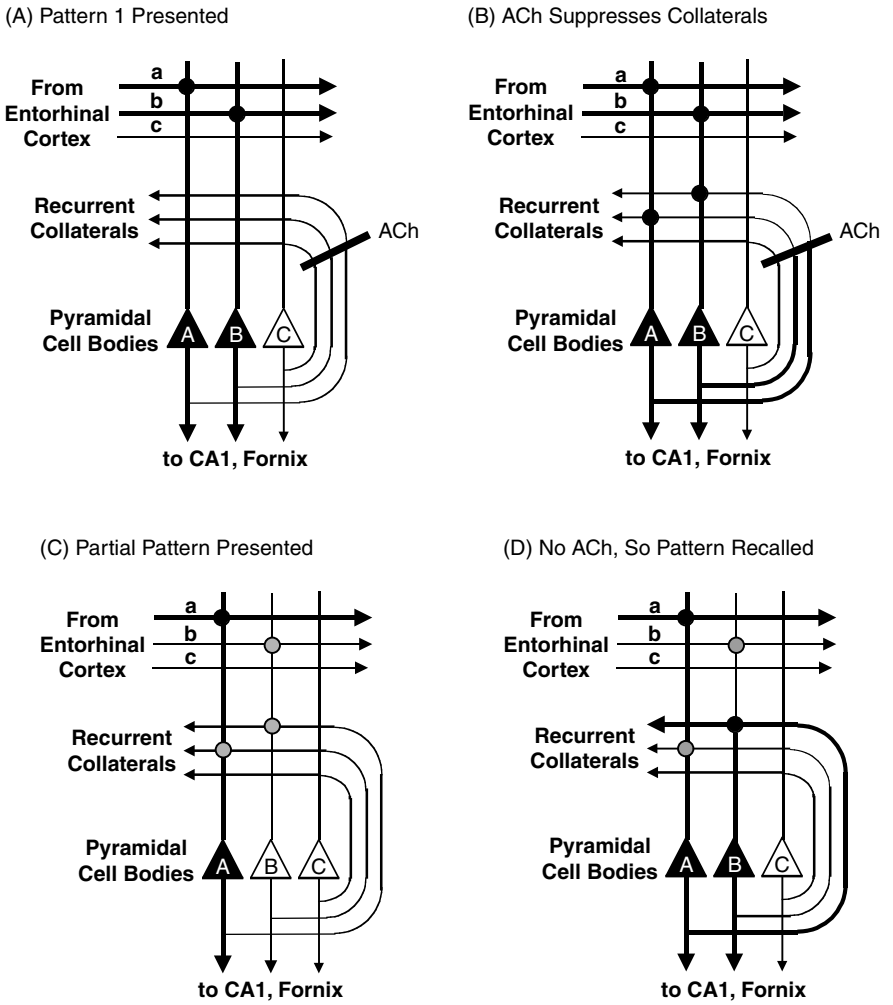

Figure 10.8 Storage of a new pattern in CA3, according to the Hasselmo model. (A) Entorhinal afferents provide information about a pattern to be stored (e.g., ab). These afferents activate a subgroup of the CA3 pyramidal cells (e.g., AB). Synapses from active entorhinal afferents to active CA3 neurons are strengthened (black circles). Acetylcholine (ACh) generally suppresses activity along recurrent collaterals. (B) Enough information passes to allow strengthening of connections between coactive CA3 neurons (gray circles) but not to activate any additional CA3 neurons. (C) When a partial version of the stored pattern is presented along the entorhinal afferents (e.g., a), this activates a subset of the CA3 neurons (e.g., A). (D) In the absence of acetylcholine, activation spreads along recurrent collaterals, activating the CA3 neurons to complete the pattern (e.g., B).

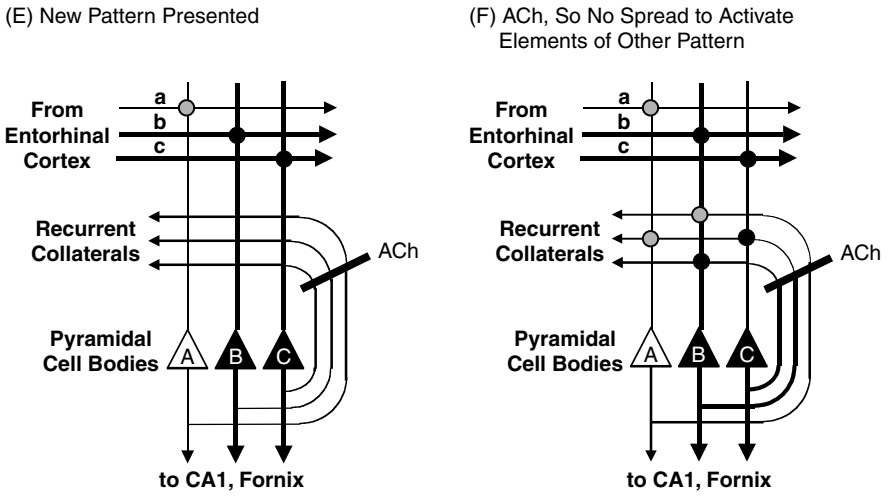

Figure 10.8 ***(continued)*** (E) A new pattern is presented for storage (e.g., bc) that shares some elements with the previously stored pattern. It activates a subset of the CA3 neurons (e.g., BC). (F) In the presence of acetylcholine (ACh), recurrent activation is not allowed to spread and activate additional neurons. Thus, although node B has a weighted connection to node A as part of the previously stored pattern, node A is not activated in the current context, and so no erroneous connection is made between A and C.

acetylcholine levels should impair the ability of the hippocampus to store new information, leading to a kind of temporary, reversible amnesia while the drug is in effect. On the other hand, because acetylcholine is not needed for recalling information in the model, cholinergic antagonists should not impair the recall of previously stored information.

This prediction has been experimentally confirmed. Rabbits and humans given the anticholinergic drug scopolamine are indeed strongly impaired in learning (storage) of new information, as was shown in figure 10.3B. However, scopolamine does not abolish execution (recall) of a trained response, indicating that the subjects can still recall previously learned information while under the influence of scopolamine.[17]

In humans, scopolamine can likewise affect the ability to learn and remember various sorts of information.[18] For example, subjects who were given scopolamine before presentation of a list of words displayed very poor performance when they were later asked to recall the words. These subjects recalled only about 6 out of 128 words, in contrast to control subjects who were not given scopolamine, who were able to recall about 45 words. However, in another study, subjects were first presented with the words, then

given scopolamine, and then asked to recall the words from the original list. For these subjects, there was no retrieval deficit; they could recall just as many words as control subjects. Together, these studies show that scopolamine selectively impairs encoding (storage) of new information but does not impair recall (retrieval) of previous information as suggested by Hasselmo's model.[19]

Cholinergic Modulation of Cortico-Hippocampal Interaction

As the preceding section described, Hasselmo has suggested that the cholinergic input from medial septum to hippocampus modulates storage in the hippocampus. Specifically, when ACh is high, the hippocampus tends to store new information; when ACh is low, the hippocampus tends to retrieve previously stored information. Another way of saying this is that the rate of hippocampal storage is proportional to the amount of ACh received.

Our cortico-hippocampal model can be extended to capture the effects of cholinergic modulation in a very straightforward way. Recall from chapter 6 that our model includes a hippocampal-region network that learns to reconstruct its inputs. In the process, new representations are formed in the internal layer that are biased to compress redundant information while preserving and differentiating predictive information. Weights in the hippocampal-region network are adjusted on the basis of the error between the input and output patterns. This adjustment can go quickly or slowly, depending on a variable in our model: a global **learning rate** (called β) specifying the magnitude of change to a weight.

Note that there are three separate and independent learning rates in our model, one corresponding to each brain region being modeled. Thus, there is one learning rate in the hippocampal-region network, one for the cortical (lower) layer of the cortico/cerebellar network, and one for the cerebellar (upper) layer of the cortico/cerebellar network; these three learning rates may be modified independently.

When the hippocampal-region network is presented with an input pattern (figure 10.9A), a representation is activated in the internal-layer nodes, which in turn activates an output pattern. This output pattern is the network's attempt to reconstruct the input. If the input pattern is familiar, the output will be an accurate reconstruction. If a novel input pattern is presented that shares some elements with a previous pattern (figure 10.9B), it may activate a similar internal representation and, in turn, generate output that is consistent with the previously learned pattern. This is the network's attempt at pattern retrieval. However, because the output is incorrect, learning occurs in

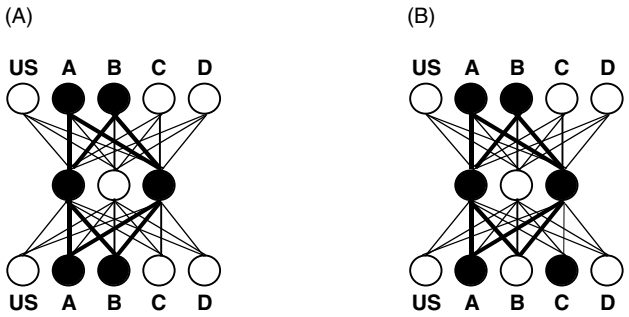

Figure 10.9 Storage versus recall in the hippocampal-region network of the cortico-hippocampal model. Activated nodes are shown as dark circles; previously strengthened connections are shown as thick lines. (A) Assume that the network has been well trained that two stimuli (A and B) are often presented together and do not predict the US. When these stimuli are presented, a particular pattern of activities is evoked in the internal layer: the representation of the compound stimulus AB. This in turn has been mapped onto outputs that reconstruct the inputs. In this case, the pattern of output activities perfectly reconstructs the inputs, and so reconstruction error is zero. (B) Now the network is presented with a new input pattern: stimuli A and C. Previously strengthened weights (thick lines) from stimulus A tend to activate the old representation, which in turn tends to activate the output pattern AB. This is incorrect: Two nodes in the output layer (B and C) have activations that do not match the input pattern, so reconstruction error equals two out of the five output nodes. At this point, learning may occur to adjust the weights to make the output look more like the input. The rate of weight change is set by the network's learning rate.

the network's weights so as to store the new pattern. This learning process causes weights to be changed to make this new pattern generate appropriate output. The magnitude of weight change on any one trial is proportional to the network's learning rate parameter. If the learning rate is high, then the network tends to always store new information. However, if the learning rate is low, the network will tend to continue to produce previous patterns in response to novel inputs.

Thus, in our model of learning in the hippocampal region, the learning rate parameter determines whether the network performs pattern storage or pattern retrieval. This is essentially the same as the storage-mediating function that Hasselmo proposes for acetylcholine. Thus, *Hasselmo's theory of ACh can be instantiated within Gluck and Myers's cortico-hippocampal model by assuming that acetylcholine from medial septum determines the hippocampal region's learning rate,* as is shown in figure 10.10.[20]

When this cholinergic input is high, hippocampal storage takes place; when the cholinergic input is absent, there is no storage at all. Between these two extremes, hippocampal storage proceeds at intermediate rates. In effect,

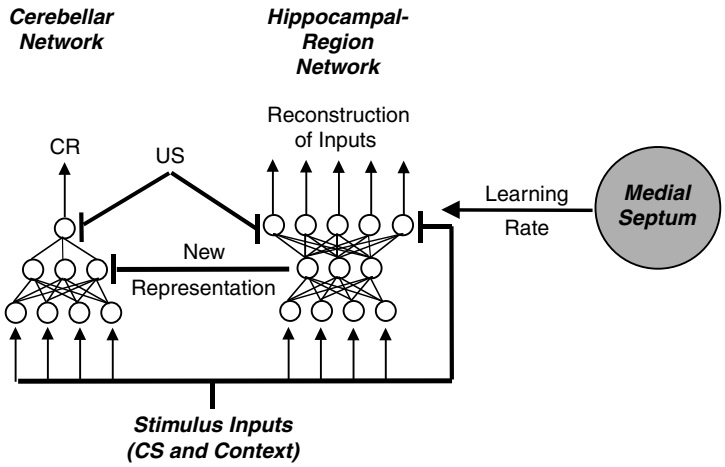

Figure 10.10 Myers et al.'s (1996) hypothesis that septohippocampal cholinergic projections modulate the amount of hippocampal storage can be implemented in the cortico-hippocampal model by assuming that the medial septum determines the hippocampal-region network's learning rate.

we have argued that the medial septum provides a "volume control" governing the degree of hippocampal learning of new stimulus representation.[21] Note that changing the hippocampal-region learning rate does not directly affect the learning rate in the cortico/cerebellar network or the rate at which hippocampal-region representations are adopted by the cortico/cerebellar network.

Cholinergic Antagonists (Scopolamine). The effect of explicitly lowering the hippocampal-region network learning rate in our model is shown in figure 10.11B. Suppose a "normal" learning rate is defined as $\beta = 0.05$. With this learning rate, the intact cortico-hippocampal model learns to respond to a CS within about 50 trials. If the learning rate is lowered by a factor of ten (to $\beta = 0.005$), learning is dramatically slower: About 125 trials are required to learn the response. The response is learned just as strongly in the end, but the system takes longer to get there. This is the same kind of slowing that is seen in rabbits that are given the cholinergic antagonist scopolamine during eyeblink conditioning: Animals that are given the drug take over twice as long to learn the conditioned response (figure 10.11A).[22] For this reason, we call the cortico-hippocampal model with the lowered learning rate a **scopolamine model;** its performance on a variety of tasks can be compared to that of animals given scopolamine.[23]

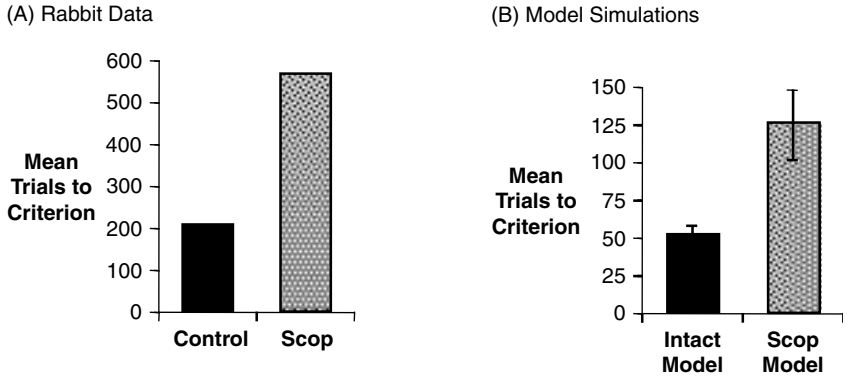

Figure 10.11 (A) The cholinergic antagonist scopolamine slows acquisition of a conditioned eyeblink response in rabbits, compared with control animals that are given an injection of saline. This is reflected in longer learning times for scopolamine (Scop) versus control animals. (Plotted from data given in Solomon et al., 1983.) A similar effect occurs in human eyeblink conditioning (Solomon et al., 1993). (B) The cortico-hippocampal model assumes that scopolamine lowers the learning rate in the hippocampal-region network. For example, whereas the hippocampal-region network in the intact model has a learning rate of $\beta = 0.05$, a scopolamine model may have a learning rate of $\beta = 0.005$. The result is that learning of a conditioned response is considerably slower in the scopolamine model than in the intact model (Myers, Ermita, et al., 1998).

In our scopolamine model, lowering the learning rate in the hippocampal-region network means that it takes longer for the model to develop new, stable stimulus representations. Because the cortico/cerebellar network—wherein long-term memories are stored and the learned response is produced—is continually working to adopt these representations, it cannot make much progress until the hippocampal region's representations have stabilized. Thus, even though learning in the cortico/cerebellar network is not slowed per se, the slow representational learning in the hippocampal-region network has the effect of retarding associative learning in the cortico/cerebellar network. However, once the hippocampal representations are stabilized, the cortico/cerebellar network can adopt these new representations—and learn behavioral responding at its normal rate. Thus, the eventual performance of the scopolamine model is just as good as the (normal) intact model; it just takes longer to get there.

Cholinergic Agonists (Physostigmine) and Dose-Response Relations. Whereas the cholinergic antagonist scopolamine slows learning, cholinergic agonists have the opposite effect. For example, **physostigmine** is a cholinergic agonist that retards the rate at which ACh is cleaned out of the synapse.

In one study, monkeys were given physostigmine and then trained on delayed nonmatch to sample (DNMS).[24] As we described in chapter 2, DNMS is a learning task in which animals see a sample object, followed by a short delay, and then must choose the novel object from a set including the original sample object. Monkeys that are given a moderate dose of physostigmine performed this task significantly better than animals that were given a low dose or no physostigmine at all, as shown in figure 10.12A. Interestingly, if the dose was high, the benefits of the drug disappeared: These monkeys learned no better than normal.

A similar phenomenon was recently shown in rabbit eyeblink conditioning.[25] Rabbits were given doses of **metrifonate,** another cholinergic agonist that works by interfering with removal of ACh from the synaptic gap. Moderate doses of metrifonate improved learning more than high doses of the drug, as is shown in figure 10.12B. In other studies, very high doses of cholinergic agonists were shown to impair learning.[26] *Thus, it appears that moderate doses of cholinergic agonists can facilitate learning, while higher doses do not facilitate learning and may even interfere with learning.*

This phenomenon may seem counterintuitive, but the cortico-hippocampal model provides an interpretation of why different doses of cholingergic agonists might have qualitatively different effects on learning. Figure 10.12C shows that lowering the hippocampal-region network's learning rate (e.g., from $\beta = 0.05$ to $\beta = 0.005$) can slow learning, whereas raising the learning rate (e.g., to $\beta = 1.0$) can facilitate learning. The faster the hippocampal-region network constructs representations, the faster these are acquired and used by the cortico-cerebellar network. However, if the hippocampal-region network's learning rate is raised still further (e.g., to $\beta = 2.0$), weights are changed so dramatically on every training trial that the hippocampal-region network begins to fluctuate wildly. It may never stabilize, or it may stabilize only after a long period. Such poor learning with an overly high learning rate is a general property of neural networks.[27] Since the hippocampal-region network never stabilizes, the cortico/cerebellar network can never stabilize either, and its ability to produce a reliable response is greatly impaired. Thus, in our cortico-hippocampal model, a very high learning rate can be just as detrimental as a very low learning rate.[28]

This principle has important implications for the development of "memory-enhancing drugs" in humans. Individuals who have chronically reduced levels of ACh—for example, after lesion to the basal forebrain structures (including medial septum)—often show improved memory function when they are given cholinergic agonists such as physostigmine.[29] Since normal aging also can reduce brain ACh levels, administering a cholinergic

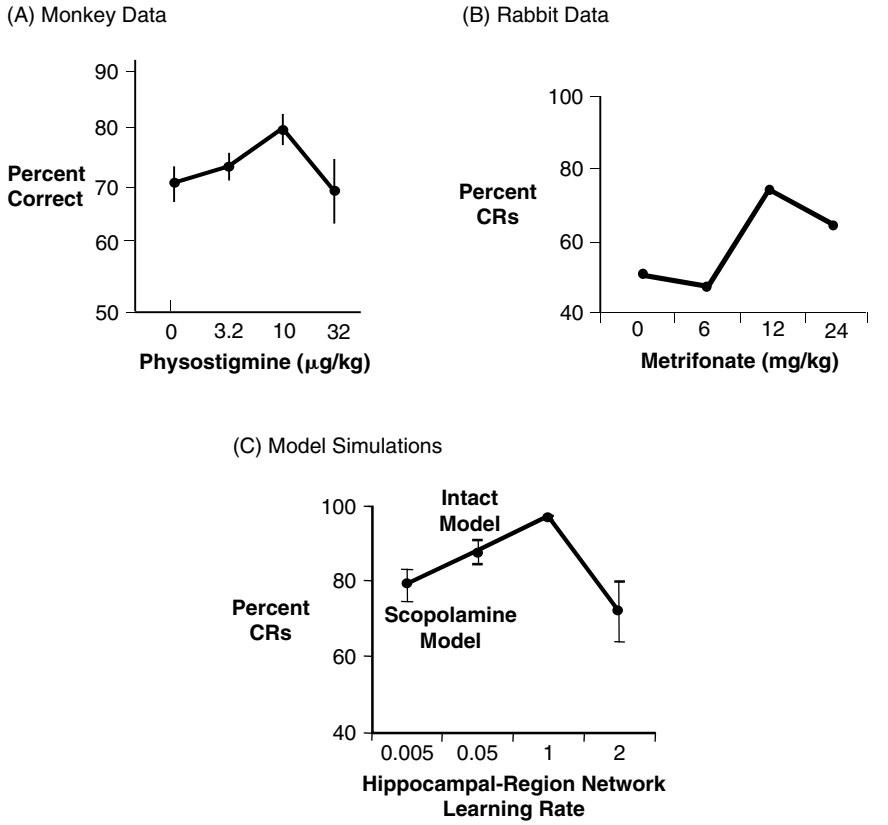

Figure 10.12 (A) Whereas a cholinergic antagonist (such as scopolamine) may slow learning, a cholinergic agonist (such as metrifonate or physostigmine) may speed learning—up to a point. Monkeys that are given a moderate dose of physostigmine (3.2 μg per 1 kg of body weight) showed improved learning compared to control monkeys that were given an injection of saline. A higher dose of physostigmine (32 μg/kg) did not improve learning (Ogura & Aigner, 1993). In other studies, high doses of physostigmine can actually impair learning (e.g., Dumery, Derer, & Blozovski, 1988; Miyamoto et al., 1989; Ennaceur & Meliani, 1992). (B) Rabbits that are given a moderate dose of metrifonate (e.g., 12 mg/kg of body weight) show faster learning than control rabbits that are given an injection of saline. Rabbits that are given a low dose (6 mg/kg) do not show the effect. A high dose of the drug (24 mg/kg) is less effective than the moderate dose. (Plotted from data presented in Kronforst-Collins et al., 1997.) (C) The cortico-hippocampal model shows a similar dose-dependent effect of increasing the hippocampal-region network's learning rate. Whereas lowering the learning rate from its normal value of $\beta = 0.05$ to $\beta = 0.005$ produces a scopolamine-like retardation in learning, increasing the learning rate to $\beta = 1.0$ produces a physostigmine-like improvement in learning. However, if the learning rate is increased too far ($\beta = 2.0$ or greater), learning begins to degrade as the hippocampal-region network becomes unstable. (A and C adapted from Myers, Ermita, et al., 1998, figure 5; B adapted from Myers et al., 1996, figure 8B.)

agonist can often improve memory in aged animals.[30] In all these cases, when brain ACh is low, a cholinergic agonist may increase the amount of available ACh and improve function. However, *in normal young subjects, whose ACh levels are presumably already optimal, further increases in ACh may not have a beneficial effect.* Thus, physostigmine given to normal young humans causes little or no improvement in memory, just as predicted by our model.[31]

Latent Inhibition and Learned Irrelevance. As we described above, our cortico-hippocampal model expects that cholinergic disruption via cholinergic antagonists will slow hippocampal-region learning. It is important to note that this is qualitatively different from the predicted effects of a hippocampal-region lesion that eliminates all hippocampal-region processing. Thus, on a behavior such as conditioned acquisition that is *not* dependent on the hippocampal region, hippocampal-region disruption (via scopolamine) may be *more* disruptive than outright hippocampal-region lesion as was seen in figure 10.3.

There is also a second, and complementary, implication of our model of cholinergic function in the hippocampal region: On behaviors that *do* require hippocampal-region processing, disruption with scopolamine may be *less* disruptive than hippocampal lesion. Scopolamine will slow hippocampal-region processing but will not eliminate it. Given enough time, the hippocampal region will still accomplish its task, and hippocampal-dependent learning will still be demonstrated, even though the entire process may be slowed.

For example, recall the phenomenon of **latent inhibition:** Prior unreinforced exposure to a cue retards subsequent learning about that cue. Our cortico-hippocampal model explains these latent inhibition behaviors in terms of redundancy compression: Cue and context are compressed together during exposure, and this impairs subsequent learning to respond to the cue but not to the context alone. Because this redundancy compression depends on the hippocampal region, damage to the hippocampal region disrupts latent inhibition (figure 10.13B).

However, we assume that scopolamine slows, but does not eliminate, hippocampal-region processing. What effect would this have on latent inhibition? During exposure, when the CS occurs in the experimental context and neither the CS nor the context predicts any US, the hippocampal region should compress their representations. Under scopolamine, this compression will proceed more slowly than normal, but it will still go on. If the exposure period is long enough, the representations of CS and

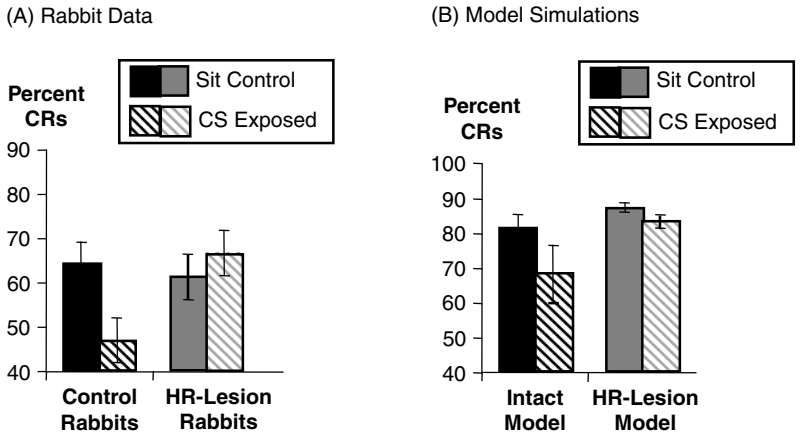

Figure 10.13 Latent inhibition: In normal rabbits, CS-US learning is slower after prior exposure to the CS (CS Exposed group) than after equivalent exposure to the context alone (Sit Control group). (A) Lesion of the hippocampal-region (including entorhinal cortex) attenuates or abolishes latent inhibition in rabbit eyeblink conditioning (Shohamy, Allen, & Gluck, 1999). (B) Similarly, there is latent inhibition in the intact model but not in the lesioned cortico-hippocampal model.

context may become just as compressed as in the normal model. Then, when the CS is paired with the US, learning will still be retarded. Under scopolamine, *any* CS-US learning is slow, of course, but prior exposure to the CS will slow learning even further. Thus, our cortico-hippocampal model expects that scopolamine should not eliminate latent inhibition (figure 10.14B).[32]

In fact, this prediction of the model appears to be borne out by data from at least one animal study: Although scopolamine slows eyeblink conditioning overall, prior exposure to the CS slows learning even further (figure 10.14A).[33]

Other studies have examined latent inhibition after injection of a toxin such as 192 IgG-**saporin,** a substance that selectively destroys cholinergic neurons. Unlike scopolamine, which merely *reduces* available ACh, saporin completely *destroys* cholinergic neurons. Thus, injecting saporin into the medial septum completely destroys the cholinergic projections to the hippocampus. In this case, the model predicts that hippocampal learning will be eliminated, and so latent inhibition will likewise be eliminated. As expected, the animals given saporin showed just this effect: Pre-exposure to the CS had no effect on subsequent CS-US learning.[34]

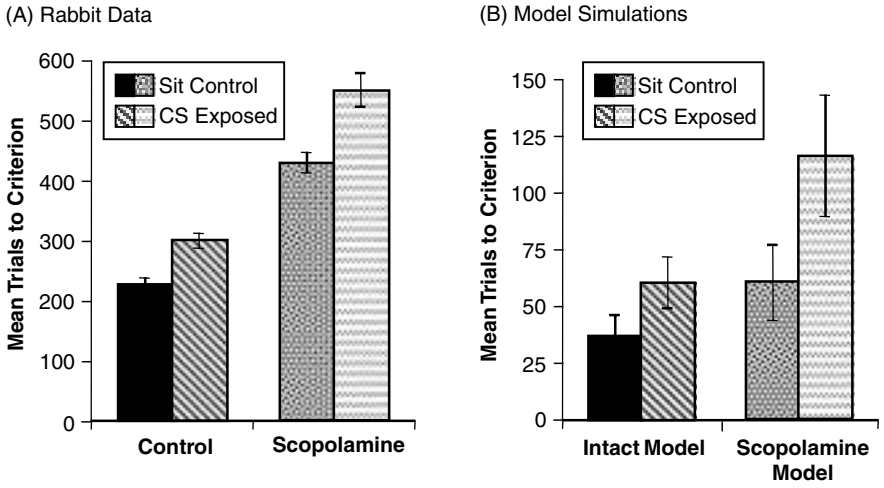

Figure 10.14 (A) The latent inhibition effect is maintained under scopolamine: Rabbits that are given scopolamine learn more slowly overall, but CS exposure slows learning still more. (Plotted from data presented in Moore et al., 1976.) (B) The cortico-hippocampal model shows a similar effect. The intact model shows latent inhibition: Exposure to the CS slows learning more than equivalent exposure to the context alone. This effect is maintained in the scopolamine model (Myers, Ermita, et al., 1998).

Learned irrelevance is a related behavioral paradigm, in which prior uncorrelated exposure to CS and US retards subsequent learning that the CS predicts the US. In previous chapters, we described data that show that learned irrelevance in rabbit eyeblink conditioning is eliminated by hippocampal-region damage (figure 10.15A). Our intact cortico-hippocampal model shows learned irrelevance because of representational changes in the hippocampal-region network; thus, learned irrelevance is also eliminated by hippocampal-region damage in our model (figure 10.15B).

Like latent inhibition, learned irrelevance is not abolished by scopolamine. In one study, experimenters administered scopolamine to a group of rabbits and then exposed them to the CS and US, uncorrelated. Later, when the effects of the drug had worn off, the rabbits received CS-US training. Learning the CS-US association was slower in these rabbits than in rabbits that had not received exposure (figure 10.16A). Thus, learned irrelevance was preserved under scopolamine.[35]

Again, our cortico-hippocampal model shows the same effect (figure 10.16B).[36] Although the hippocampal network is slowed by scopolamine during the exposure phase, representational changes do eventually occur. These are sufficient to slow later CS-US learning.

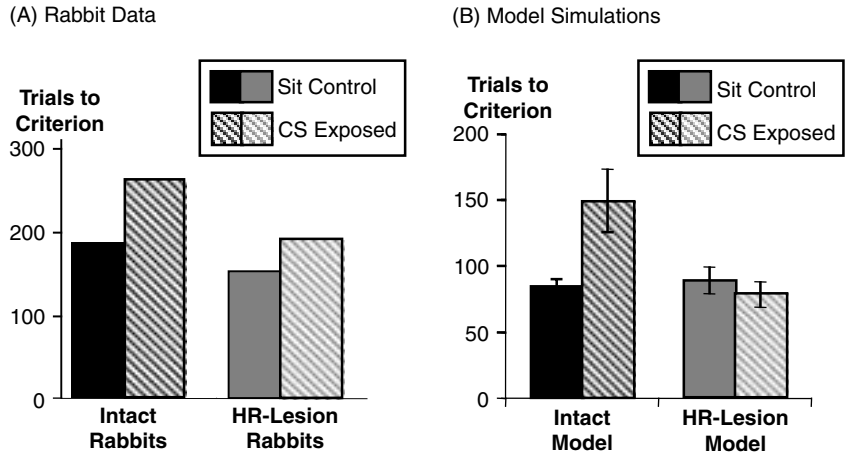

Figure 10.15 Learned irrelevance is the phenomenon whereby prior uncorrelated exposure to CS and US slows subsequent CS-US association. (A) Hippocampal-region damage (specifically entorhinal lesion) disrupts learned irrelevance in rabbit eyeblink conditioning. (B) The cortico-hippocampal model shows the same effect. (A is from Allen, Chelius, & Gluck, 1998.)

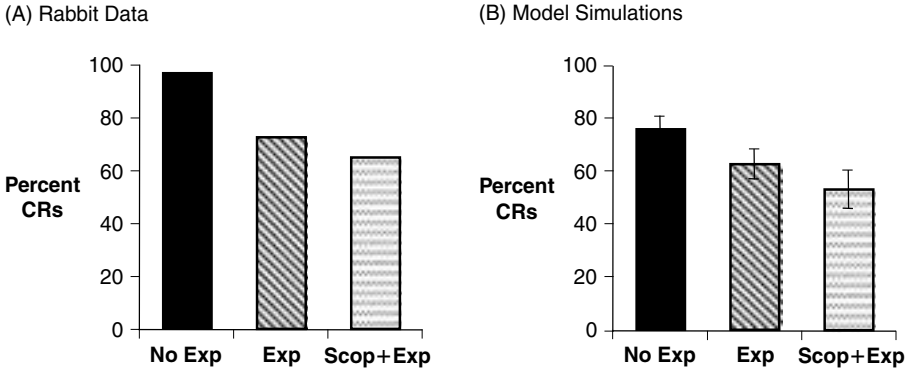

Figure 10.16 (A) Scopolamine does not disrupt learned irrelevance. Among rabbits that are given a control injection, exposure to uncorrelated CS and US (Exp group) slows subsequent CS-US learning relative to a group that received equivalent exposure to the context alone (No Exp group). To test the effects of scopolamine, rabbits were given uncorrelated exposure to CS and US while under the influence of the drug (Scop+Exp group); later, when the drug had washed out, these rabbits showed learning that was just as slow as or slower than that of the Exp group. (Plotted from data presented in Harvey et al., 1983.) (B) The cortico-hippocampal model shows the same effect. The intact model shows learned irrelevance: Uncorrelated exposure to CS and US slows subsequent learning, compared with simulations that were given equivalent exposure to the context alone. If the hippocampal-region network's learning rate is lowered during exposure (Scop+Exp condition), learning is still slowed. (Plotted from data presented in Myers, Ermita, et al., 1998.)

Scopolamine and the Hippocampus. All the empirical data reported so far involve **systemic administration** of drugs, meaning that a drug is injected into the bloodstream or otherwise allowed to spread throughout the body. This means that the drug could be acting at any of a number of places, since cholinergic receptors are located throughout the brain and throughout the body. We have assumed that the important effects are taking place in the cholinergic projections from medial septum to hippocampus, but this is only an assumption in dealing with a drug that has been administered throughout the body and brain.

What is needed is a way to determine whether the important effects of scopolamine really take place in the medial septum and hippocampus. One way to investigate this is by combining drug studies with selective lesion studies. If scopolamine disrupts learning by disrupting cholinergic projections from medial septum to hippocampus, then scopolamine should have no effect in a hippocampal-lesioned subject.

This prediction of our model has also been verified in rabbit eyeblink conditioning:[37] Rabbits with hippocampal-region damage learn a conditioned response at the same speed with and without scopolamine (figure 10.17A). Again, our cortico-hippocampal model shows the same effect, as is seen in figure 10.17B.[38] These data on the effects of scopolamine in lesioned animals are in contrast to the effects of the same drug in intact animals and the intact model (figures 10.17C&D, reproduced from figure 10.11).

In our model, the effect of scopolamine is to retard hippocampal-region learning. If the hippocampal region is removed, then scopolamine has no effect on learning in the model. Thus, the empirical data and model behavior are consistent in implicating scopolamine as acting to disrupt hippocampal processing.

A second way to investigate where scopolamine has its effect is to administer the drug via localized injection to a particular brain region. Of course, any drug that is so injected may well spread somewhat to adjacent areas, particularly if the injection size is large and the brain area is small; still, this is a more precise method than systemic administration. Here, the questions of interest are: What happens when a cholinergic antagonist such as scopolamine is directly injected to the hippocampus? And what if it is injected directly to the medial septum? Our cortico-hippocampal model predicts that *any* interference with septal-hippocampal cholinergic processes might retard learning.

Up to a point, this has been shown to be the case. Scopolamine that is injected directly into the medial septum does slow eyeblink conditioning.[39] Scopolamine that is injected into the nearby lateral septum, which does not

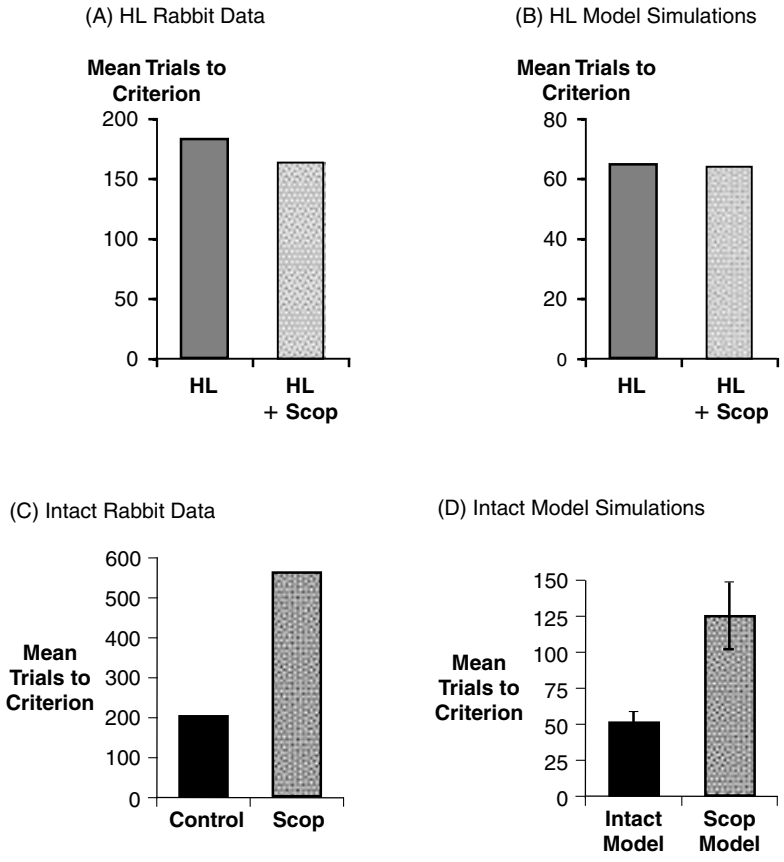

Figure 10.17 (A) Scopolamine does not retard eyeblink conditioning in rabbits with hippocampal lesion (HL). (Plotted from data presented in Solomon et al., 1983.) (B) Since the scopolamine model involves reduced hippocampal-region network learning rates, it is also trivially true that scopolamine does not affect learning in the HR-lesion model. Compare to Figure 10.11A, reprinted here as (C). The cholinergic antagonist scopolamine slows acquisition of a conditioned eyeblink response in rabbits, compared with control animals that are given an injection of saline. This is reflected in longer learning times for scopolamine (Scop) versus control animals. (Plotted from data given in Solomon et al., 1983.) A similar effect occurs in human eyeblink conditioning (Solomon et al., 1993). (D) The cortico-hippocampal model assumes that scopolamine lowers the learning rate in the hippocampal-region network. For example, whereas the hippocampal-region network in the intact model has a learning rate of $\beta = 0.05$, a scopolamine model may have a learning rate of $\beta = 0.005$. The result is that learning of a conditioned response is considerably slower in the scopolamine model than in the intact model (Myers, Ermita, et al., 1998). (A and B are adapted from Myers, Ermita, et al., 1998, figure 10.)

project to the hippocampus, does not affect eyeblink conditioning.[40] Thus, the medial septum does seem to be critically involved in the effects of scopolamine on learning.

However, when scopolamine was injected directly into the hippocampus, eyeblink conditioning was not slowed.[41] At first glance, this result appears to suggest that the hippocampus is *not* the site where scopolamine has its effect.

There are several possible explanations for this anomalous empirical finding. The first is that these studies did not inject scopolamine throughout the hippocampus, but only in the dorsal hippocampus; this is approximately the top half of the "C" formed by the hippocampus (figure 10.18; also refer to figure 8.2A). However, in rabbits, large portions of the septohippocampal cholinergic projection terminate in the ventral hippocampus.[42] It is possible that dorsal injections disrupted cholinergic function in one half of the hippocampus but left enough ACh in the lower (or ventral) hippocampus to allow learning. We conjecture that if the experiments were repeated, with scopolamine injected throughout the hippocampus, the hippocampus might be sufficiently disrupted to impair learning.

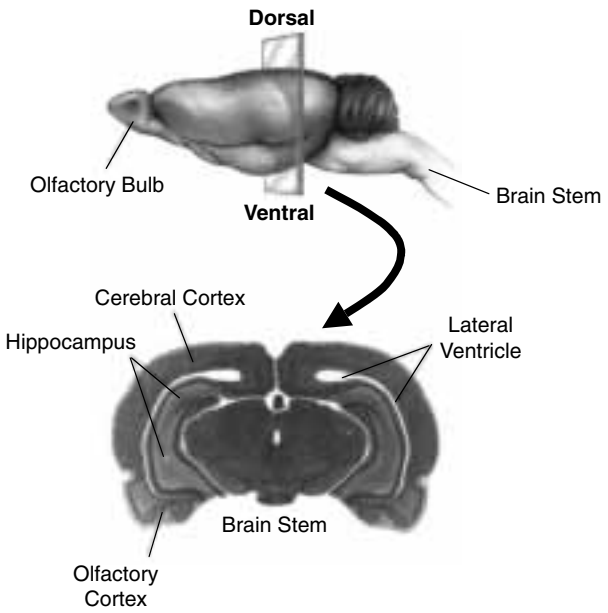

Figure 10.18 Top: Drawing of the rat brain, showing placement of the slice shown below. Bottom: Slice through the rat brain. At this point, the hippocampus has a long vertical extent and a rough "C" shape. A "dorsal" hippocampal lesion would remove only the top half of the "C," while a "ventral" lesion would destroy the lower half. The white areas are fluid-filled ventricles. Dark regions are cell bodies. (Adapted from Bear, Connors, & Paradiso, 1996, p. 179.)

A second possible interpretation of the anomalous result is that scopolamine may not be the correct kind of drug to use for a study of hippocampal cholinergic processes. ACh, like many neurotransmitters, can activate a number of different kind of receptors, and various kinds of receptors respond differentially to different experimental drugs. Thus, a drug which blocks (or activates) one receptor type may not affect another receptor type. Cholinergic receptors come in two basic classes, called **muscarinic** and **nicotinic** receptors. These receptor types are so named because the chemical muscarine activates the first type while nicotine activates the second type. (This is a purified version of the nicotine found in tobacco products.) In contrast, the brain's natural ACh activates both types of receptors.

Scopolamine primarily blocks muscarinic receptors but has little effect on nicotinic receptors. The hippocampus has both muscarinic and nicotinic receptors, and only the muscarinic receptors would be blocked by scopolamine, leaving the nicotinic receptors to function normally. Perhaps the mediation of these nicotinic receptors is enough to allow learning even after the muscarinic receptors are blocked by scopolamine.[43] Thus, it might be important to try to replicate the experiment using a drug (or a cocktail of drugs) that blocks both muscarinic and nicotinic receptors. In contrast, when scopolamine is injected to the medial septum, this may reduce the overall levels of ACh provided to the hippocampus, which would reduce the activation of both muscarinic and nicotinic receptors.

In sum, then, despite a considerable amount of prior work, there is still need for further studies to confirm the exact mechanisms by which scopolamine impairs learning and the locations at which scopolamine has its strongest effects. Nonetheless, the idea that cholinergic disruption retards hippocampal learning, thereby retarding conditioning, seems to account for a broad range of existing data as well as being consistent with many anatomical and physiological observations.

Who Modulates the Modulator?

The previous section described how acetylcholine may modulate network dynamics in hippocampal field CA3 (and elsewhere), determining whether storage or retrieval dominates. But this begs an important question: How is the level of acetylcholine determined? How does the system know whether the pattern of inputs present along the extrinsic afferents represents a new pattern to be stored or a degraded version of an old input that should be retrieved from memory?

One clue comes from the finding that there is also a path from hippocampus *back* to medial septum.[44] When this hippocampal-septal pathway is

electrically stimulated, this causes a decrease in medial septal activity.[45] This implies that activity in the hippocampus can turn off the medial septum, thereby cutting off the septohippocampal projections of ACh.

Hasselmo and colleagues have suggested that this backprojection forms a self-regulating feedback loop in hippocampal field CA1.[46] We will not go through the details of the CA1 model here,[47] but the basic idea includes the assumption that CA1 performs a comparison function: noting whether the output from CA3 matches the original entorhinal input.[48] When they do match, this indicates that the pattern has been successfully stored in CA3. When they differ, either the pattern is novel or it is incompletely stored; in either case, storage should be enabled.

Figure 10.19A illustrates Hasselmo's idea in which a familiar pattern is presented along the entorhinal inputs. CA3 responds, and CA1 compares this response against the original entorhinal inputs. If the match is good, CA1 activity is high. CA1 then inhibits the medial septum, which reduces ACh. Low ACh corresponds to recall mode, in which the recurrent collaterals connections between neurons are allowed to reverberate and storage is disabled.

However, if a novel pattern is presented along the entorhinal inputs—as shown in figure 10.19B—CA3 responds as best it can, and CA1 notes that this response is a poor match to the entorhinal inputs. CA1 activity drops, ceasing its inhibition of medial septum. The medial septum springs to life, projecting ACh to hippocampus. High ACh corresponds to storage mode in which the recurrent collaterals are suppressed and the new pattern is stored.

Hasselmo's model of feedback regulation of septohippocampal ACh is still a hypothesis that needs to be fully tested. However, one behavioral result is consistent with the model: Medial septal neurons respond strongly when an animal is presented with novel but not familiar stimuli—just as is expected by Hasselmo's model.[49]

Moreover, Hasselmo's self-regulation theory lends itself naturally to being incorporated into our cortico-hippocampal model of conditioning. Earlier in this chapter, we described how ACh levels could be functionally interpreted as hippocampal learning rates within the cortico-hippocampal model.*[50] More recently, we have extended this modeling to incorporate Hasselmo's ACh self-regulation theory into the cortico-hippocampal model.[51] The mismatch between CA3 output and entorhinal input proposed by Hasselmo as a

*Technically, the neurons recorded by Wilson and Rolls were in the diagonal band of Broca; this is a group of cells lying next to the medial septum in the basal forebrain. The diagonal band of Broca and medial septum appear to function as a single processing unit, and the fact that they are distinguished with different names may be misleading.

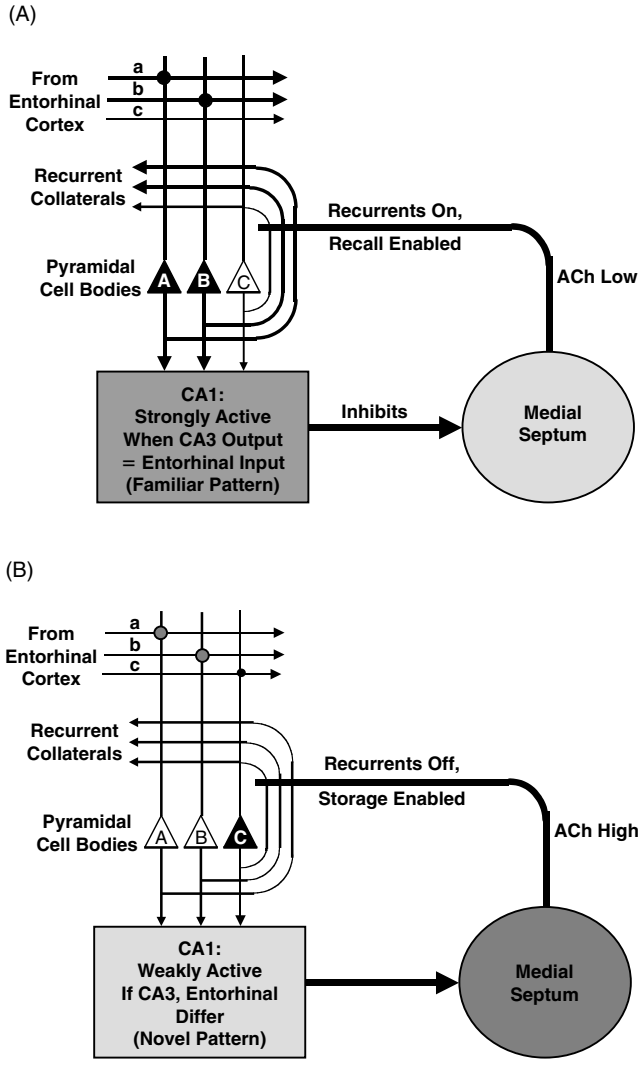

Figure 10.19 Hasselmo's hypothesis about hippocampal self-regulation of cholinergic modulation. (A) In brief, hippocampal field CA1 acts as a comparator of CA3 and entorhinal inputs. If they match, this implies that the pattern is well stored in CA3. CA1 activity is high and inhibits the medial septum. This decreases the level of ACh projected from medial septum to hippocampus. Low ACh corresponds to the recall mode: The recurrent collaterals are enabled, and pattern completion is permitted. (B) Alternatively, if the CA3 output is not a good match for the entorhinal input, this implies that the input pattern is new—or at least insufficiently stored. CA1 activity drops, the medial septum is released from inhibition, and ACh is projected to hippocampus. High ACh corresponds to the storage mode: The recurrent collaterals are disabled, and storage proceeds.

function for CA1 is very much like what happens in our autoencoder network when inputs and outputs are compared. As in Hasselmo's theory of CA1 as a novelty detector, the cortico-hippocampal model's autoencoder generates an input/output mismatch for novel stimuli.

We are currently analyzing a self-regulating version of the cortico-hippocampal model, based on Hasselmo's ACh self-regulation theory, in which the autoencoder mismatch error drives increases medial-septal activity, raising the hippocampal learning rate. Preliminary analyses of this generalized version of the cortico-hippocampal model indicate that it is consistent with both behavioral data on conditioning and electrophysiological data on medial septal activity during conditioning.[52] Interestingly, this biologically based model of learning rate regulation is very similar to algorithms that have previously been proposed within the neural network literature for optimizing network performance.[53]

10.3 OTHER THEORIES AND ISSUES

The models that we discussed in the previous section focus on the cholinergic projection from medial septum to hippocampus and how it can modulate hippocampal learning rates. This section reviews two related issues. First, acetylcholine is not the only chemical involved in the projection from medial septum to hippocampus; there are also neurons that project the neurotransmitter **GABA** (gamma-aminobutyric acid). This neurotransmitter may play an important role in how medial septum modulates hippocampal function. Second, acetylcholine functions as a neuromodulator in cortex, as well as in the hippocampus. Some of the same principles underlying cholinergic modulation of hippocampus may apply to cortex as well.

Finally, although this chapter focuses on neuromodulation involving ACh, it is important to note that ACh is not the only neuromodulator that affects hippocampal function. Other neuromodulators have received less study in terms of their effect on learning and memory, but one in particular—dopamine—has recently been the focus of interesting empirical and computational work. The interested reader is particularly referred to a model of dopamine modulation in predicting reward[54] and of norepinephrine in modulating sensitivity to behavioral context.[55]

Septohippocampal GABAergic Projections

As we mentioned above, the medial septum projects GABA as well as ACh to the hippocampus.[56] When the medial septum is lesioned or disrupted, this

GABAergic projection to hippocampus is also affected. Thus, some of the effects of septal damage or disruption may also reflect loss of GABAergic modulation in the hippocampus.

GABA is the major inhibitory transmitter in the brain, meaning that it tends to reduce activity in the postsynaptic neuron. In the hippocampus, GABA can be thought of as a neuromodulator that causes global changes in hippocampal processing. Specifically, the GABAergic septohippocampal projection is important in the generation of **theta rhythm,** a phenomenon in which large numbers of hippocampal neurons begin to fire in synchronous bursts, approximately four to eight times a second. Although the firing of any one neuron results in a minuscule electric charge, the synchronized activity of many thousands of neurons causes an electric charge large enough to be detected through the scalp. A procedure that records these group effects is the **electroencephalogram (EEG).** Figure 10.20 shows examples of an EEG recorded from a rat, during theta rhythm versus during a period of unsynchronized firing. During theta rhythm, periodic waves of GABA from medial septum arrive in the hippocampus. In turn, hippocampal pyramidal neurons go through rhythmic cycles of activity and inactivity.

In an animal such as a rat, theta rhythm typically occurs during exploratory behaviors, such as walking, rearing, and sniffing. Nonsynchronized firing occurs during consummatory behaviors, when the animal is sitting quietly and eating, drinking, or grooming. Perhaps not coincidentally, during exploratory behaviors, an animal has to organize and remember incoming

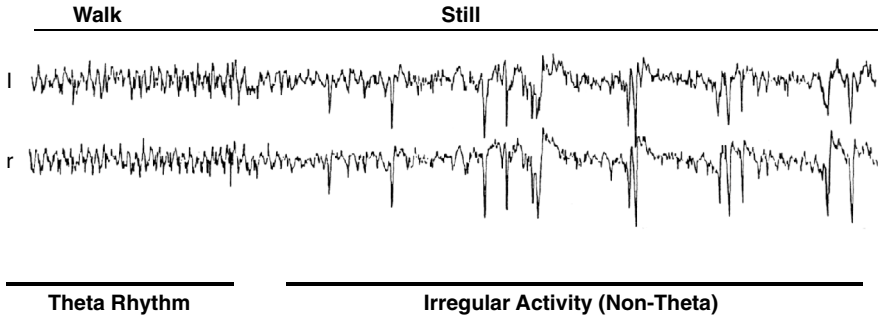

Figure 10.20 EEG recordings from hippocampal field CA1 in a rat during about 13 seconds; for the first 3 or 4 seconds, the rat was walking, and during the final 6 or 7 seconds, the rat was still. The top trace shows neuronal activity recorded from the left (l) hippocampus, and the lower trace is from the right (r) hippocampus. When the animal was walking, both traces showed regular, fast theta rhythm. When the animal became still, the trace showed large, irregular non-theta activity. (Adapted from Buzsáki, 1989, figure 1.)

sensory information—comparable to a learning or storage phase. By contrast, consummatory behaviors provide relatively less incoming sensory information and would be a good time for the brain to work on organizing and consolidating previous information.

György Buzsáki has interpolated from these data to propose that the two stages of neuronal activity might correspond to two different aspects of learning.[57] In brief, Buzsáki's theory proposes that theta rhythm occurs during exploration and other learning behaviors when new information is bombarding the brain and is being temporarily stored in the hippocampus. Theta rhythm serves the purpose of rhythmically silencing the hippocampus, breaking the steady stream of inputs into manageable 200-msec packets of information. Once exploration stops, there is time for the brain to "catch its breath" and analyze this information. The pattern of neural activity at this point is consistent with a recall and consolidation process: Recently active hippocampal neurons become active again and cause activation in the same entorhinal cells that excited them previously. This may allow the information that was temporarily stored in the hippocampus to be transferred out to cortical areas for long-term storage.

In short, Buzsáki's theory suggests that GABAergic septohippocampal inputs modulate hippocampal processing between storage (theta) and consolidation (non-theta). There is an obvious parallel between this theory and Hasselmo's proposal that cholinergic septohippocampal inputs modulate hippocampal processing between storage (high ACh) and recall (low ACh) states.

While GABA is a fast-acting neurotransmitter, the effects of ACh are slower. How do they interact? Perhaps slow-acting ACh might set the overall framework in which storage can occur: putting the hippocampus into a storage mode or a recall mode. Once the hippocampus is in storage mode, fast-acting GABA induces theta rhythm, modulating the storage of individual pieces of information. In this way, both cholinergic and GABAergic modulation might each contribute an important function to hippocampal dynamics (table 10.1).

Whether or not the relationship conjectured in table 10.1 is true, it is clear that an important avenue of future research will be to determine exactly how GABAergic and cholinergic inputs interact. Computational modeling may prove helpful here as a means of exploring prospective interactions.[58]

Cholinergic Modulation in Cortex

As we noted previously, acetylcholine projects throughout the brain and body. Near the medial septum in the basal forebrain is another group of cells, the

Table 10.1 Possible Synchrony Between ACh and GABA in Modulating Hippocampal Dynamics

	Exploring	Resting State
Observable Behavior	Incoming information to process and store	Little incoming information
Hippocampus	Rapidly *store* new information	*Recall* and consolidate to cortex
Acetylcholine	*High* → Enable hippocampal storage	*Low*→ Enable hippocampal recall
GABA	*Theta rhythm:* Break input into manageable packets	*Non-Theta activity:* Associated with recall and consolidation

nucleus basalis, which projects ACh throughout cortex (refer to figure 10.2). Just as acetylcholine promotes plasticity in the hippocampus, it also promotes plasticity in cortex. And just as acetylcholine suppresses extrinsic inputs more than intrinsic inputs in hippocampus, there is evidence that it behaves the same way in cortex.[59] This leads to the idea that if ACh modulates information storage in hippocampus, it might have a similar function in cortex. This would suggest that just as the medial septum drives hippocampal storage, cholinergic projections from nucleus basalis could drive cortical storage.

Recall from chapter 8 that stimulus representations in sensory cortex expand and shrink, depending on the meaning of stimuli. In particular, if a stimulus is paired with a US, its representation tends to expand, while the representations of other stimuli may compress to make room. Important (meaningful) stimuli win a larger portion of the cortical map. The available evidence suggests that the cortex does not know what kind of US a particular stimulus might be associated with, only that the stimulus is somehow significant. Apparently, some other parts of the brain are responsible for recognizing the CS-US association and signaling the cortex to adapt its stimulus representations accordingly.

Areas such as the amygdala are known to receive information about CS and US pairings and may be responsible for forming associations between them. These areas project to the nucleus basalis. Therefore, one plausible hypothesis is as follows: *When a CS is paired with a US, the amygdala (or other brain areas) activate the nucleus basalis, which in turn delivers acetylcholine to cortex, enabling cortical remapping to enlarge the representation of that CS.*[60]

If this hypothesis is true, then stimulating the nucleus basalis should cause cortical remapping. Several studies have shown just such an effect. When a tone CS is paired with nucleus basalis stimulation—instead of a real US—the

representation of the CS in primary auditory cortex expands.[61] Additionally, when the nucleus basalis is lesioned or the cholinergic projections are otherwise disrupted, cortical plasticity is greatly reduced.[62]

These findings are very exciting, not least because of their implications for rehabilitation after cortical damage. Perhaps it may eventually even be possible to use judicious stimulation of the nucleus basalis to encourage cortical remapping in individuals who have lost the use of one cortical area. For now, though, we turn to some more immediate implications for human memory disorders.

10.4 IMPLICATIONS FOR HUMAN MEMORY AND MEMORY DISORDERS

Understanding cholinergic modulation of brain function is important with respect to understanding how normal learning and memory occur. Cholinergic modulation is disrupted in clinical syndromes that damage the basal forebrain, potentially damaging projections both from medial septum to hippocampus and from nucleus basalis to cortex. Understanding cholinergic modulation and its disruption in these syndromes may help in the development of pharmacological treatment and rehabilitation techniques.

Basal Forebrain Damage Following Cerebral Aneurysm

In rare instances, an individual may suffer selective damage to one or more basal forebrain structures, disrupting cholinergic projections with little collateral damage to nearby brain areas.[63] These individuals offer an opportunity for researchers to study how the human brain responds to loss of these cholinergic projections.

More often, the basal forebrain may be among the structures that are damaged in a stroke. A **stroke** occurs when blood flow is interrupted, through either occlusion (blockage) or rupture of a blood vessel. In either case, brain areas downstream, which depend on that blood vessel to supply oxygen and nutrients, are deprived; in the extreme, cells in the deprived areas will die. In an **aneurysm,** the walls of the blood vessel are weakened and may balloon out under pressure of the blood flow (figure 10.21A); in the extreme, the aneurysm may rupture. One of the most common sites of cerebral aneurysm is the **anterior communicating artery (ACoA),** a small blood vessel that interconnects the right and left anterior cerebral arteries. The ACoA provides oxygen and nutrients to the basal forebrain and frontal cortex (figure 10.21B), and ACoA aneurysm is a frequent cause of basal forebrain damage in humans.

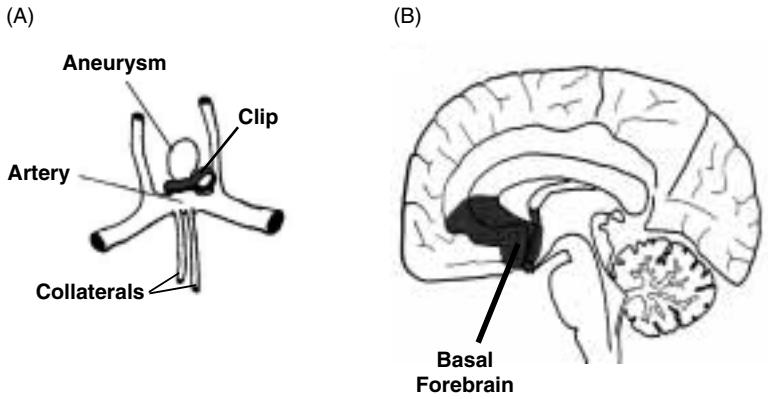

Figure 10.21 (A) An aneurysm is a weakening of the wall of an artery; under pressure of blood flow, the wall may balloon out. If the balloon ruptures, blood will leak out, decreasing blood flow in the artery. Structures downstream of the aneurysm, which depend on that artery for blood and nutrients, will be deprived. Surgery to repair an aneurysm may involve implanting a small clip at the neck of the aneurysm, preventing rupture and leakage. Blood resumes flowing through the artery and into the collateral branches that direct blood to its destinations. (B) The anterior communicating artery (ACoA) vascularizes a variably sized region that can include basal forebrain and parts of the frontal cortex. ACoA aneurysm and rupture can result in damage to these regions.

About 85% of individuals who survive ACoA aneurysm recover well enough to return to work or normal life, but about 5–15% have long-lasting impairments. The cluster of symptoms is called **ACoA syndrome,** and there are three basic components: (1) anterograde amnesia, (2) personality changes (such as loss of self-control, unpredictable aggression, or apathy), and (3) confabulation, or the spontaneous production of false memories.* Which components an individual displays and their severity may depend on the precise degree to which various brain structures have been damaged.

The anterograde amnesia that can follow ACoA aneurysm is superficially similar to the amnesia that follows medial temporal damage—except that the

*Confabulation should be distinguished from lying, in which an individual deliberately attempts to mislead others; confabulators are genuinely unaware that their memories are inaccurate. Confabulation should also be distinguished from false memory syndrome, in which an otherwise normal individual suddenly "remembers" a supposedly repressed memory of childhood abuse or other trauma. Confabulation is a clinical syndrome resulting from brain injury. A typical instance of confabulation would be if a patient, asked what he had for breakfast, gave a perfectly reasonable response (e.g., "cereal and toast") that just happened to be wrong.

ACoA aneurysm survivors have no direct hippocampal damage. This component of ACoA syndrome is believed to result from basal forebrain damage, which may disrupt hippocampal function in humans, much as it does in animals.[64] The animal studies—along with drug studies and computational modeling—suggest that the behaviorally superficial similarity between individuals with damage to the hippocampal-region lesion and damage to the basal forebrain lesion may be illusory. Underneath, the two amnesic syndromes may have subtle but important differences.

For example, recall that whereas direct hippocampal lesion spares eyeblink conditioning in rabbits, medial septal lesion impairs it. Similarly, humans and animals that are given the anticholinergic drug scopolamine show retarded eyeblink conditioning. Accordingly, we expected that ACoA amnesia, which involves basal forebrain damage, would also impair eyeblink conditioning. If so, this would be in contrast to the finding of spared eyeblink conditioning in medial temporal amnesia.

Recently, we have had the opportunity to test a small population of individuals who became amnesic following ACoA aneurysm. When we tested these individuals on the eyeblink conditioning paradigm, they showed a severe impairment relative to age-matched control subjects, as is shown in figure 10.22.[65] In contrast, individuals with medial temporal amnesia show relatively normal eyeblink conditioning.[66] Thus, eyeblink conditioning ap-

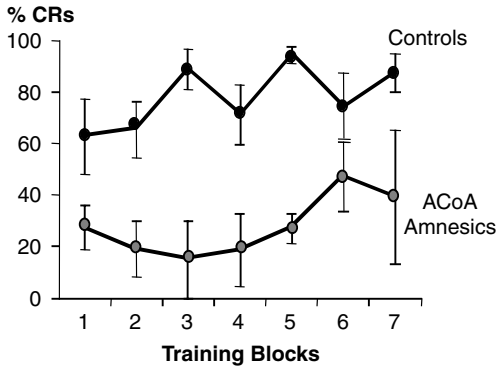

Figure 10.22 Eyeblink conditioning in individuals who became amnesic following aneurysm of the anterior communicating artery (ACoA) is strongly impaired relative to matched control subjects. The ACoA amnesics have presumed damage to basal forebrain, including medial septum and nucleus basalis. Their performance is in marked contrast to the performance of amnesic subjects with medial temporal (hippocampal-region) damage, who condition normally. (Drawn from data presented in Myers, DeLuca, et al., in preparation.)

pears to discriminate between amnesia caused by hippocampal-region damage and hippocampal disruption. These findings are exactly as predicted by the animal data and by our computational modeling.

This finding has important clinical implications. Although basal forebrain damage and hippocampal damage can both cause amnesia, the two amnesic syndromes are not identical. Eyeblink conditioning is differentially affected by the two lesion types, and other kinds of learning may be, too. Accordingly, patients with different etiologies may respond to different kinds of therapy, and a clinician might make use of this information to optimize rehabilitation programs.

Cholinergic Depletion in Alzheimer's Disease

As we described in chapter 9, **Alzheimer's disease (AD)** is a degenerative disease of the brain that leads to cognitive impairments, particularly memory decline. One anatomical hallmark of AD is the dysfunction and death of basal forebrain neurons, leading to cholinergic depletion throughout the brain.[67] Other neuromodulators, including dopamine, norepinephrine, and serotonin, are also reduced in the AD brain, but the cortical cholinergic systems seem to be affected earlier and to a greater extent than the other systems.

Cholinergic depletion may underlie some of the cognitive impairments associated with AD.[68] There is some similarity between the kinds of memory impairments seen in individuals who are given cholinergic antagonists (such as scopolamine) and individuals in the early stages of AD,[69] although scopolamine does not reproduce all of the symptoms of AD.[70]

If cholinergic depletion is responsible for some of the symptoms associated with AD, then administration of cholinergic agonists should provide some relief from these symptoms. In fact, some limited memory improvement has been observed in Alzheimer's patients who are given cholinergic agonists such as tacrine (brand name Cognex), physostigmine, or donepezil (trade name Aricept).[71]

The effectiveness of these drugs tends to be modest and short-lived; symptoms may be temporarily ameliorated but not reversed.[72] Additionally, there are often side effects: Liver and gastrointestinal problems are common in individuals taking tacrine. The limited success of cholinergic agonists in treating AD indicates that cholinergic depletion is only one piece of the AD puzzle.

On the other hand, the fact that cholinergic agonists have any success at all confirms that cholinergic systems do play an important role in AD.

Computational models of cholinergic modulation and AD may lead to a better understanding of the role of ACh in normal learning and in dementia.

SUMMARY

- Various neuromodulators, including acetylcholine (ACh), alter how neurons transmit messages—without altering the content of the message. The major cholinergic input to the hippocampus is from the medial septum in the basal forebrain.
- Disrupting the septohippocampal cholinergic projection (by damage to medial septum or through drugs that affect synaptic transmission of ACh) can lead to devastating memory impairment, presumably by disrupting hippocampal function. ACh depletion is also implicated in the memory impairments of Alzheimer's disease.
- Whereas direct hippocampal region spares classical conditioning, septohippocampal disruption impairs classical conditioning; thus, the effects of disrupting the hippocampus can be worse than outright removal.
- Hasselmo and colleagues, noticing that ACh has different effects on extrinsic than intrinsic inputs, suggested that ACh acts to modulate hippocampal dynamics between a storage mode and a recall mode.
- Building on this idea, we suggested that septohippocampal cholinergic input could specifically act to modulate hippocampal-region learning rates. This was implemented in the cortico-hippocampal model and accounted for the effects of various cholinergic drugs on classical conditioning.
- Other neuromodulators also have effects on learning; GABA from medial septum to hippocampus may also mediate hippocampal storage, while ACh from nucleus basalis to cortex may be important in cortical plasticity and the development of topographic maps.

APPENDIX 10.1 SIMULATION DETAILS

The computational model presented in section 10.2B was originally described in Myers, Ermita, et al. (1998). Full details of this model are given there (see also Myers et al., 1996).

In brief, the cortico-hippocampal model is generally the same as that described in other chapters (e.g., chapters 6 and 7). The hippocampal-region learning rate is set to a fixed parameter: $\beta = 0.05$ on trials in which the US is present and $\beta = 0.005$ on trials in which the US is absent. To simulate the

effects of moderate doses of a cholinergic antagonist such as scopolamine, the hippocampal-region learning rate is decreased tenfold (i.e., $\beta = 0.005$ on trials in which the US is present and $\beta = 0.0005$ on trials in which the US is absent). To simulate the effects of high doses of a cholinergic agonist such as physostigmine, the hippocampal-region learning rate is increased (e.g., $\beta = 1.0$ on trials in which the US is present and $\beta = 0.1$ on trials in which the US is absent). No other parameters in the model are assumed to be altered by administration of these cholinergic drugs.