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A Computational Model of Cholinergic Disruption of Septohippocampal Activity in Classical Eyeblink Conditioning

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A previous neurocomputational model of corticohippocampal interaction (Gluck & Myers, 1993) can provide a framework for examining the behavioral effects of septohippocampal modulation during classical conditioning. The model assumes that the hippocampal region is necessary for forming new stimulus representations during learning, but not for the formation of simple associations. This paper considers how septohippocampal interaction could affect this function. The septal nuclei provide several modulatory inputs to the hippocampus, including a cholinergic input which Hasselmo (1995) has suggested may function to regulate hippocampal dynamics on a continuum between two states: a storage state in which incoming information is encoded as an intermediate-term memory and a recall state when this information is reactivated. In this theory, anticholinergic drugs such as scopolamine should disrupt learning by selectively reducing the hippocampus's ability to store new information. An approximation of Hasselmo's idea can be implemented in the corticohippocampal model by a simple manipulation of hippocampal learning rate; this manipulation is formally equivalent to adjusting the amount of time the hippocampus spends in learning and recall states. With this manipulation, the model successfully accounts for the effects of scopolamine in retarding classical conditioning in humans (Solomon, Groccia-Ellison, Flynn, Mirak, Edwards, Dunehew, & Stanton, 1993) and animals (Solomon, Solomon, van der Schaaf, & Perry, 1983). The model further predicts that although cholinergic agonists (such as Tacrine) may improve learning in subjects with artificially depressed brain acetylcholine levels, there may be limited memory improvement in normal subjects from such cholinergic therapy. This is consistent with the general finding of a U-shaped dose response curve for cholinergic drugs in normal subjects: low to moderate doses may improve learning, but higher doses are ineffective or even degrade learning (e.g., Ennaceur & Meliani, 1992; Dumery, Derer, & Blozovski, 1988; etc.).

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INTRODUCTION

In this paper, an existing computational model of corticohippocampal interaction in associative learning (Gluck & Myers, 1993; Myers & Gluck, 1994) is extended to include the effects of septohippocampal modulation. In particular, the model is generalized to incorporate the ideas proposed by Hasselmo and Schnell (1994) that the septohippocampal pathways modulate hippocampal processing states. The resulting model provides a framework for examining the relative behavioral effects of hippocampal lesion, compared with hippocampal disruption via disrupting these septohippocampal pathways, as by the anticholinergic drug scopolamine. Such indirect hippocampal disruption often impairs learning more than direct hippocampal damage (Solomon, Solomon, van der Schaaf, & Perry, 1983).

For example, a canonical form of simple learning in both animals and humans is classical conditioning of the eyeblink response. In this preparation, a previously neutral stimulus such as a tone or light (the conditioned stimulus or CS) is repeatedly paired with a blink-evoking corneal airpuff (the uncondi-

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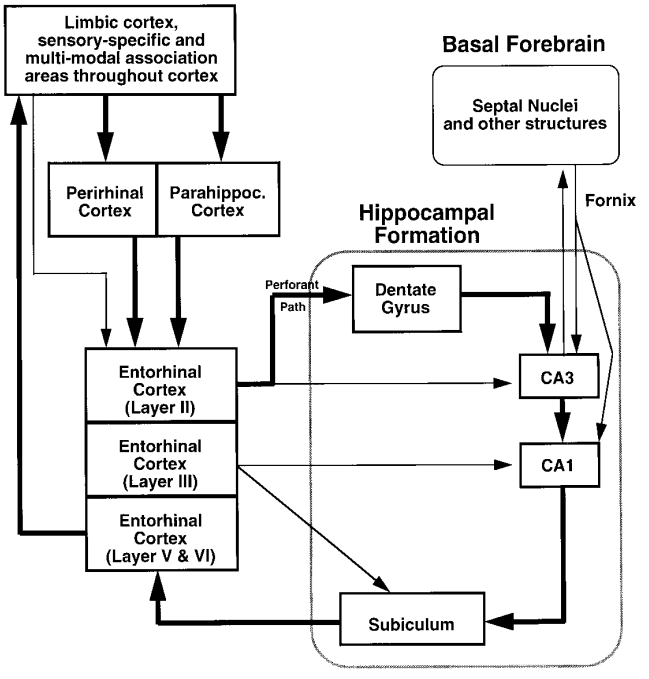

FIG. 1. Schematic of major information pathways in the hippocampal region. Sensory information arrives through the superficial entorhinal cortex, travels through the hippocampal formation (dentate gyrus, CA3, CA1, subiculum), before exiting through the deep entorhinal cortex to the sensory and association areas where it originated. There is a second hippocampal input–output pathway through the fornix; among the structures with reciprocal hippocampal connections through the fornix is the basal forebrain, containing several nuclei including the medial septum.

tioned stimulus or US); with repeated pairings, the subject acquires a CS–US association such that presentation of the CS alone can elicit an anticipatory blink. This preparation has been used to study learning in humans (Solomon, Groccia-Ellison, Flynn, Mirak, Edwards, Dunehew, & Stanton, 1993), rabbits (Gormezano, Kehoe, & Marshall, 1983; Thompson, 1986, 1990), and rats (Schmajuk, Lam, & Christiansen, 1994). Under optimal experimental parameters, damage to the hippocampal region (Fig. 1) does not impair eyeblink conditioning in rabbits (Port & Patterson, 1984; Schmaltz & Theios, 1972), rats (Schmajuk et al., 1994), or humans (Gabrieli, McGlinchey-Berroth, Carrillo, Gluck, Cermak, & Disterhoft, 1995; Woodruff-Pak, 1993; Daum, Channon, & Canavan, 1989; Weiskrantz & Warrington, 1977). This spared learning contrasts with the characteristic anterograde amnesia for many other kinds of learning which follows hippocampal damage in animals and humans (Squire, 1992; Cohen, 1984). However, eyeblink conditioning may be disrupted by hippocampal-region damage if there are more complex temporal or correlational relationships between CSs and US (e.g., Solomon & Moore, 1975; Moyer, Deyo, & Disterhoft, 1990). These data suggest that although the hippocampal region may not be required for simple CS–US association learning, it is required for learning more complex stimulus–stimulus relationships.

These data are correctly accounted for by the corticohippocampal model (Gluck & Myers, 1993). That model assumes that the hippocampal region is required for learning about stimulus–stimulus regularities in the environment, but not for simpler associations such as underlie basic eyeblink conditioning. The model correctly expects no particular deficit in simple acquisition of a CS–US association, but significant disruption to more complex conditioning paradigms (Gluck & Myers, 1993). It also accounts for the disruption in contextual learning which can follow hippocampal region damage (Myers & Gluck, 1994) and for the finding that human hippocampal-damaged amnesics show normal performance early in training of a probabilistic categorization task, but with extended training control subjects outperform the amnesics (Knowlton, Squire, & Gluck, 1994).

So far, this computational model has centered on the hippocampal region and its cortical inputs, especially the pathway for stimulus information to enter and exit the hippocampus via the entorhinal cortex (cf. Myers, Gluck, & Granger, 1995). But the hippocampus has other important connections, including modulatory input. One such structure, the medial septum, sends a strong cholinergic input to the hippocampus (Hasselmo, 1995; Nolte, 1993; Nauta & Feirtag, 1986) and may also modulate the theta rhythm, a hippocampal EEG rhythm associated with exploratory behaviors (Berry & Thompson, 1979; Buzsaki & Eidelberg, 1983). Damage to the medial septum should interrupt these pathways and may therefore interrupt hippocampal function indirectly. Medial septal lesion greatly retards acquisition of simple eyeblink conditioning (Berry & Thompson, 1979), while pharmacological disruption of cholinergic processes in the medial septum, through cholinergic antagonists such as scopolamine, similarly disrupts conditioning in rabbits (Solomon et al., 1983) and humans (Solomon et al., 1993). These data imply that disrupting the hippocampus, through septal damage, may have a more devastating effect than merely removing the hippocampus through outright lesion (Solomon et al., 1983).

These data can be addressed in the corticohippocampal model by incorporating a recent suggestion that the septohippocampal pathways modulate the relative amount of information storage and retrieval in the hippocampus (Hasselmo & Schnell, 1994).

This can be done by simply manipulating relative storage rates in the model and does not require further theoretical assumptions. The resulting system correctly shows no hippocampal-lesion impairment but a strong septal-lesion impairment; it can also account for the dose-dependent effects of cholinergic intervention in septal processing. One important prediction of the model is that although drugs which improve cholinergic processing may improve learning in patients with damage to medial septal nuclei and other cholinergic nuclei in the basal forebrain region, there is expected to be only a limited improvement in normal subjects with normal brain acetylcholine levels. This prediction has important implications, given the recent pharmacological interest in the production of "memory drugs" to improve learning in normal subjects.

REVIEW OF THE CORTICOHIPPOCAMPAL MODEL

Gluck and Myers (1993) previously presented a computational model of hippocampal function in associative learning. Central to this model is the definition of a *stimulus representation* as a pattern of activities over a set of neurons (or nodes in a connectionist network) which recode a stimulus input (example activity patterns are shown in Fig. 2). The exact form of this pattern is arbitrary and may bear little resemblance to the stimulus which evokes it; all that matters is that some responses are strong and others are weak. Learning about stimuli is then equivalent to associating their representations with appropriate behavioral outputs. If the representations of two stimuli are very distinct (as in Figs. 2A vs. 2B), it will be very easy to map them to different behavioral responses. If the representations are very similar (as in Figs. 2B vs. 2C), it is harder to map them to different responses. Learning to associate stimuli with responses can therefore be facilitated by choosing appropriate stimulus representations. Gluck and Myers (1993) proposed that the hippocampal region can facilitate learning in this way. Specifically, the hippocampal region is assumed to modify stimulus representations according to two biases: *predictive differentiation,* a bias to make representations more distinct if stimuli are to be mapped to different responses, and *redundancy compression,* a bias to make representations more similar if stimuli cooccur or are redundant. Other regions such as cerebellar and cerebral cortices, which are assumed to be the sites of long-term memory storage, cannot modify stimulus representations by themselves; these other regions can, however, adopt the new representations formed in the hippocampal region.[2]

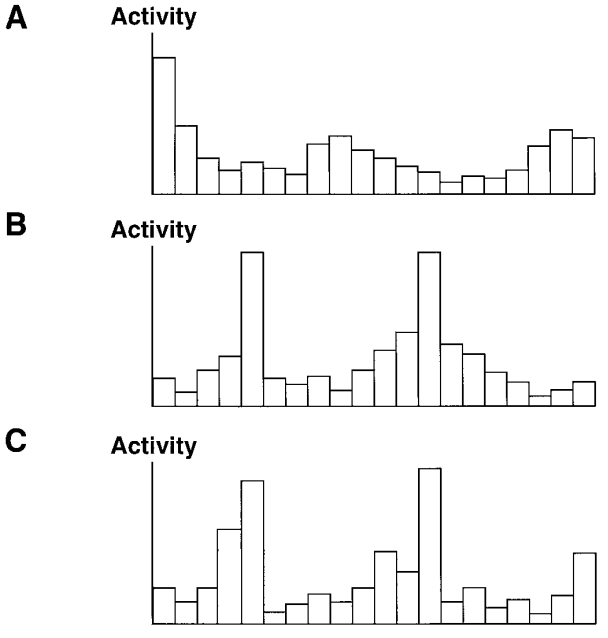

FIG. 2. Schematic examples of stimulus representations. (A) Presenting a stimulus input results in a particular representation, or pattern of activities, over a set of neurons or nodes. The exact pattern of activations may have little superficial similarity to the inputs that evoke them, but some nodes will respond strongly and others will respond weakly, resulting in an arbitrary pattern. (B) A different input will evoke a different representation which may overlap little with the one shown in (A); if so, it will be easy to map the representations to different outputs and hence, to learn different responses to the two inputs. (C) By contrast, if a stimulus evokes a very similar representation to that shown in (B), it will be harder to map these two stimuli to different responses. The similarity between two representations may reflect physical similarity between the two stimuli, or other correlations.

These ideas have been implemented in a connectionist model of classical conditioning (see Fig. 3A), with one network representing learning dependent on the hippocampal region and a second network representing cortical long-term storage (Gluck & Myers, 1993). The hippocampal-region network is a predictive autoencoder (Hinton, 1989; Baldi & Hornik, 1989), which learns a transform from inputs representing conditioned and contextual stimuli, through a narrow hidden layer, to outputs which reconstruct the inputs as well as a prediction of reinforcement (US) arrival. Because the internal layer in this network is constrained to be smaller than the

[2] It should be noted that the hippocampus may either temporarily store these new representations or merely be required for their construction elsewhere. Our present model does not distinguish these possibilities with respect to associative learning.

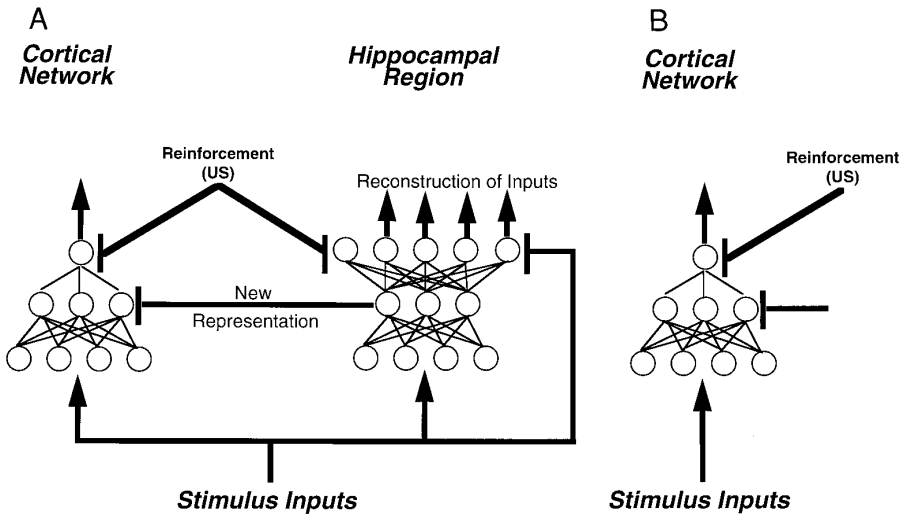

FIG. 3. The corticohippocampal model (Gluck & Myers, 1993). (A) The intact model. One network, representing processing dependent on the hippocampal region, learns to reconstruct its inputs, plus a prediction of US arrival, while forming new stimulus representations in its internal layer which compress redundant information but differentiate predictive information. A second cortical network is assumed to be the site of long-term memory. This network learns to map from its inputs to an internal representation provided by the hippocampal-region network and from those representations to an output which is assumed to govern strength (or probability) of a behavioral response. The strength of the response is also a measure of US prediction by the system. (B) The lesioned model. Disabling the hippocampal-region network is assumed to result in the cortical network no longer being able to acquire new (hippocampal-dependent) representations, although it can still learn to map from existing representations to new behavioral responses.

input and output layers, the network is forced to compress redundant information while preserving predictive information. The result is that a representation develops in the internal layer which has exactly the properties required by the theory.

By contrast, the cortical network is not assumed to be able to form new representations in its internal layer. It can, however, adopt the representations formed in the hippocampal network. It then learns to map from these representations to an output; the strength or probability of a behavioral response is assumed to be a function of the strength of this output—which is also a measure of how strongly US arrival is anticipated, given the current inputs.

In this model, hippocampal lesions are simulated by disabling the hippocampal network (see Fig. 3B). In this case, no new hippocampal-dependent stimulus representations can be formed, although the cortical network is left with whatever representations were present before lesioning, and it can still learn to map from these preexisting representations to new behavioral responses.

This model can be used to model the acquisition of a simple conditioned eyeblink response. Hippocampal-region damage does not impair conditioned eyeblink acquisition in humans (Gabrieli et al., 1995; Woodruff-Pak, 1993; Daum et al., 1989; Weiskrantz & Warrington, 1979), rabbits (Solomon & Moore, 1975; Solomon, 1977; Akase, Alkon, & Disterhoft, 1989), or rats (Schmajuk et al., 1994). Figures 4A and 4B summarize these data. The model correctly expects no lesion deficit on acquiring the conditioned response (Fig. 4C). The model assumes that hippocampal-region damage eliminates the ability to form new stimulus representations, but not the ability to learn new stimulus–response mappings based on preexisting representations. Therefore, the lesioned model shows no particular deficit in acquisition of a simple CS–US association (Gluck & Myers, 1993).

By contrast with the situation for simple acquisition, the model predicts that the hippocampal region should be critical for more complex conditioning paradigms which require information about stimulus–stimulus relationships. For example, in sensory preconditioning, prior exposure to a cue compound increases the amount by which learning to one of the cue components generalizes to the other cue component (Thompson, 1972). The model predicts that this enhanced generalization arises from representational compression of the two components during the preexposure phase. Thus, the intact but not lesioned corticohippocampal model shows sensory preconditioning (Gluck & Myers, 1993); this is consistent with data showing that hippocampal-region damage eliminates sensory preconditioning in rabbit eyeblink conditioning (Port & Patterson, 1984). Similarly, the model correctly accounts for observed im-

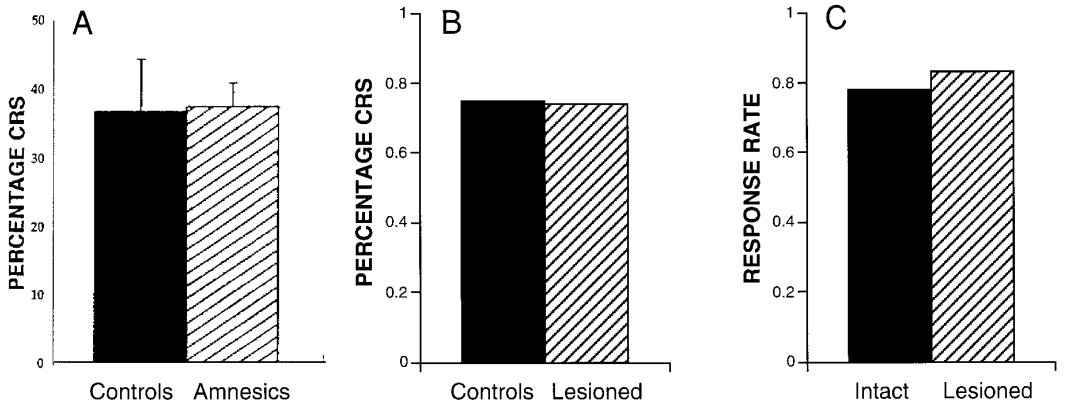

FIG. 4. Hippocampal-region damage does not affect acquisition of conditioned eyeblink responding in (A) humans (reprinted from Gabrieli et al., 1995) or (B) rabbits (after Solomon & Moore, 1975). (C) Similarly, the corticohippocampal model does not expect any lesion deficit on conditioned acquisition.

pairments after hippocampal-region damage in latent inhibition and reversal learning (Gluck & Myers, 1993); the model makes several novel predictions, including impairments in compound preconditioning and easy–hard transfer (Gluck & Myers, 1993). The model also provides an interpretation of the impairments in contextual processing seen after hippocampal-region damage (Myers & Gluck, 1994). Finally, with straightforward generalizations, the same model can be applied to human probabilistic category learning (Knowlton et al., 1994) and rodent simultaneous odor discrimination (Myers & Gluck, 1995), and correctly predicts the behavior of hippocampal-damaged amnesic patients.

SEPTOHIPPOCAMPAL MODULATION

The corticohippocampal model has centered on the hippocampal region and its cortical inputs, especially the pathway for stimulus information to enter and exit hippocampus via the entorhinal cortex (cf. Myers et al., 1995). But the hippocampus has other important connections, which may modulate its processing. One region which communicates with hippocampus is the basal forebrain, including nucleus basalis, diagonal band, and medial septum. The basal forebrain is an important source of the neurotransmitter acetylcholine (ACh) throughout the cortex, with the medial septum in particular sending acetylcholine to the hippocampus (Hasselmo, 1995; Nolte, 1993; Nauta & Feirtag, 1986). Acetylcholine within the central nervous system is a neuromodulator which has been shown to have several important effects in hippocampus and cortex, including suppression of synaptic transmission (Hasselmo & Schnell, 1994), enhancement of pyramidal cell excitability through suppression of currents underlying adaptation (Barkai & Hasselmo, 1994; Madison, Lancaster, & Nicoll, 1987), and enhancement of synaptic modification (Hasselmo & Barkai, 1995; Huerta & Lisman, 1993).

An important aspect of this cholinergic suppression of synaptic transmission in the hippocampus and elsewhere is that it is selective, affecting some kinds of synapses more strongly than others. For example, acetylcholine strongly blocks intrinsic recurrent collaterals in stratum radiatum of hippocampal region CA3 (Hasselmo, Schnell, & Barkai, 1995) and the Schaeffer collaterals in stratum radiatum of hippocampal region CA1 (Hasselmo & Schnell, 1994), but has a much weaker effect on external inputs from entorhinal cortex in region CA1 (Hasselmo & Schnell, 1994). Thus, cholinergic suppression has more effect on intrinsic, recurrent collaterals than on external afferents.

Hasselmo (1995) has interpreted this effect as suggesting a means whereby the dynamics of the hippocampus could vary on a continuum between two modes for the *storing* of new information or the *recall* of previously stored information. The high degree of recurrency within region CA3 has led several researchers to suggest that this region could function as an autoassociative network (e.g., Marr, 1971; McNaughton, 1989; Treves & Rolls, 1992; O'Reilly & McClelland, 1994; Hasselmo et al., 1995). Autoassociative networks store input patterns by adapting weighted connections ("synapses") on recurrent collaterals; later, when presented with a partial or degraded version of a stored pattern, the network can retrieve the original pattern by allowing iterative spread of activation along the recurrent collaterals (e.g., Anderson, 1977; Kohonen, 1984). However,

such a network needs to function in two different modes. First, during storage, the recurrent collaterals need to be suppressed, to prevent recall of previously stored information from interfering with new storage. Later, during pattern recall, the recurrent collaterals need to be active, to allow previously stored information to be reconstructed. Hasselmo et al. (1995) suggested that cholinergic modulation would be able to perform this function in CA3. When acetylcholine is present, it selectively suppresses intrinsic recurrent collaterals, allowing a storage phase; when it is absent, the recurrent collaterals are allowed to be active and reconstruct patterns. As patterns are reconstructed, they may then be presented to the neocortex for storage there. Hasselmo and Schnell (1994) propose a similar role for cholinergic modulation in heteroassociative memory function in CA1, and cholinergic modulation has been integrated in a large-scale computational model of the hippocampus combining associative memory function in those regions with self-organization of afferent input from the entorhinal cortex (Hasselmo & Stern, 1995). According to this account, eliminating cholinergic modulation through septal lesion, or disrupting it through pharmacological intervention, should disrupt hippocampal function by reducing the ability to store new information and increasing the tendency to recall old memories when presented with new ones. This might lead to a dramatically different pattern than outright hippocampal lesion, which would simply eliminate the ability both to store and recall patterns.

It should be noted that, in addition to cholinergic inputs, GABAergic inputs from the medial septum may also be involved in mediating hippocampal theta rhythm (Berry & Thompson, 1979; Buzsaki & Eidelberg, 1983). Hippocampal EEG operates in two distinct modes: alternating periods of theta waves, rhythmic (4–8 Hz) oscillations, and sharp waves, characterized by nonrhythmic bursting activity (Fox, Wolfson, & Ranck, 1983). Theta waves occur during exploratory behavior such as walking and sniffing, while sharp waves occur during such consummatory behaviors as grooming and eating (Vanderwolf & Leung, 1983). Buzsaki (1989) has suggested that this alternation between theta and sharp-wave states corresponds to two phases of hippocampal-system processing: theta representing a "storage" phase, in which incoming information is stored in the hippocampus (fast but volatile storage), and sharp waves indicating a "recall" or "consolidation" phase, during which stored hippocampal memories are reinstated for gradual transfer to neocortex (slow but long-term storage). Again, a septal lesion which disrupts theta would be expected to reduce the ability to store information in the hippocampus. Thus, although this account of septohippocampal interaction differs from Hasselmo's in the mechanisms discussed, it makes the same qualitative prediction regarding the effects of septal lesion on hippocampal processing.

In fact, septal lesion does disrupt hippocampal processing behaviorally and greatly retards acquisition of conditioned eyeblinking in rabbits (Berry & Thompson, 1979; Salvatierra & Berry, 1989; Powell, Milligan, & Buchanan, 1976), as shown in Fig. 5A. Septal lesion of course interrupts all septohippocampal connections, cholinergic as well as GABAergic processes. The cholinergic processes can be selectively targeted, through pharmacological intervention, such as administration of the cholinergic antagonist scopolamine, which blocks muscarinic receptors (Brazhnik, Vinogradova, Stafekhina, & Kitchigina, 1993a). Scopolamine delivered directly to medial septum greatly retards eyeblink conditioning in rabbits (Solomon & Gottfried, 1981), as shown in Fig. 5B.

Systemically administered scopolamine similarly delays eyeblink conditioning in humans (Solomon et al., 1993) and rabbits (Solomon et al., 1983), as shown in Fig. 5C. Systemic atropine, another antimuscarinic, retards rabbit eyeblink conditioning as well (Downs, Cardozo, Schneiderman, Yehle, VanDercar, & Zwilling, 1972). Conditioning in hippocampal-lesioned animals is not retarded by scopolamine (Solomon et al., 1983), suggesting that the drug acts directly or indirectly to affect hippocampal processing. This is supported by neurophysiological data showing that systemic scopolamine acts to alter hippocampal EEG rhythms and reduce neural responsiveness in hippocampus (Salvatierra & Berry, 1989). Systemic scopolamine, of course, interrupts other cholinergic processes, such as those arising from nucleus basalis and reticular formation, and other cholinergic targets, such as neocortex (cf. Izquierdo, 1989). However, these other afferents and targets appear to be of lesser importance in eyeblink conditioning than the septohippocampal pathways: lesions of nucleus basalis alone do not affect eyeblink conditioning (Ginn & Powell, 1992), while nucleus basalis–cortical cholinergic processes apparently do not play a critical role in memory (cf., Kesner, 1988). Therefore, it appears that systemic scopolamine has its greatest effect on eyeblink conditioning in disrupting septohippocampal cholinergic processes.[3]

[3] Intrahippocampal injections of scopolamine have been shown to retard rabbit eyeblink conditioning in one study (Solomon &

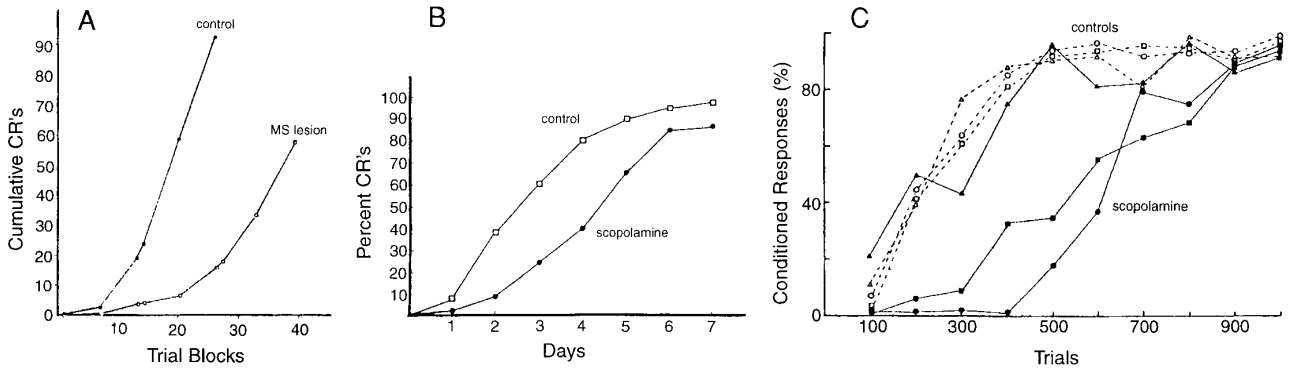

FIG. 5. Medial septal disruption disrupts conditioning of eyeblink response in the rabbit. (A) Direct medial septal lesion (adapted from Berry & Thompson, 1979). (B) Application of the anticholinergic drug scopolamine to the medial septum (adapted from Solomon & Gottfried, 1981). (C) Systemic application of scopolamine (adapted from Solomon et al., 1983). In (B) and (C), the effect of scopolamine is to delay the onset of conditioning, rather than preventing it. Conditioning in (A) does not extend to asymptotic performance in controls, so it is undetermined whether the lesioned animals eventually reach normal performance levels.

The behavioral results shown in Fig. 5 all replicate a basic result that the onset of conditioned learning is delayed after medial septal disruption. However, in each case, learning with the dysfunctional septohippocampal system is not abolished, merely delayed (cf., Salvatierra & Berry, 1989). Once conditioning begins to emerge, learning appears to proceed at a normal rate, and eventually the scopolamine groups in Figs. 5B and 5C reach the same asymptotic performance levels as controls. The lesioned animals in Fig. 5A were not trained to asymptotic performance, but their responding might also have continued to increase given further training.

MODELING SEPTOHIPPOCAMPAL INTERACTION

How can these effects of septohippocampal disruption be incorporated within Gluck and Myers's (1993) corticohippocampal model? Assume that the medial septum regulates the amount of time that the hippocampus spends storing new information, by the presence of cholinergic inputs, as suggested by Hasselmo, or by the theta rhythm, as suggested by Buzsaki, or by some combination of the two. Septal disruption or lesion should then reduce or prevent storage of new information, but might not affect the rate at which stored information is recalled and transferred to cortical long-term storage sites. This is schematized in Fig. 6A.

In the corticohippocampal model, the amount of storage in the hippocampal-region network is governed by the learning rate parameter in that network. The rate at which information is transferred from hippocampus to cortical storage is governed independently by the learning rate on the lower layer of the cortical network. Therefore, altering the hippocampal learning rate is equivalent to selectively reducing hippocampal storage without affecting hippocampal recall and transfer to cortex. Thus, this simple mechanism of adjusting hippocampal learning rate is enough to affect processing in qualitatively the way hypothesized by Hasselmo to occur after septal damage. Figure 6B schematizes this approach.

There is another way to effect disruption of hippocampal storage in the corticohippocampal model: namely, to assume that septal damage reduces the amount of time the hippocampus spends storing new information, but not the amount of time it spends recalling old information. The hippocampal network is formalized as an autoencoder, which attempts to reconstruct its inputs on its output layer. Familiar (well-stored) patterns should be reconstructed perfectly. But novel patterns should have some reconstruction error—particularly given the tendency of this and all autoassociative networks to treat novel

Gottfried, 1981), which would suggest that the effects of scopolamine are in the septum or septohippocampal pathways rather than in the hippocampus itself. However, other studies have shown that posttraining injections of intrahippocampal scopolamine do retard recall of avoidance learning and habituation (Jerusalinsky, Cervenansky, Walz, Bianchin, & Izquierdo, 1993; Izquierdo, da Cunha, Rosat, Jerusalinsky, Ferreira, & Medina, 1992), though not of conditioned emotional responding (Brioni & Izquierdo, 1988). Thus, the effects of intrahippocampal scopolamine vary for different tasks. Within the eyeblink preparation, however, it seems that intrahippocampal scopolamine is less disruptive than septal or systemic scopolamine, reinforcing the suggestion that the relevant effects occur afferent to the hippocampus and are sited either in the septohippocampal pathways themselves or in the medial septum, which would in turn disrupt septohippocampal processes.

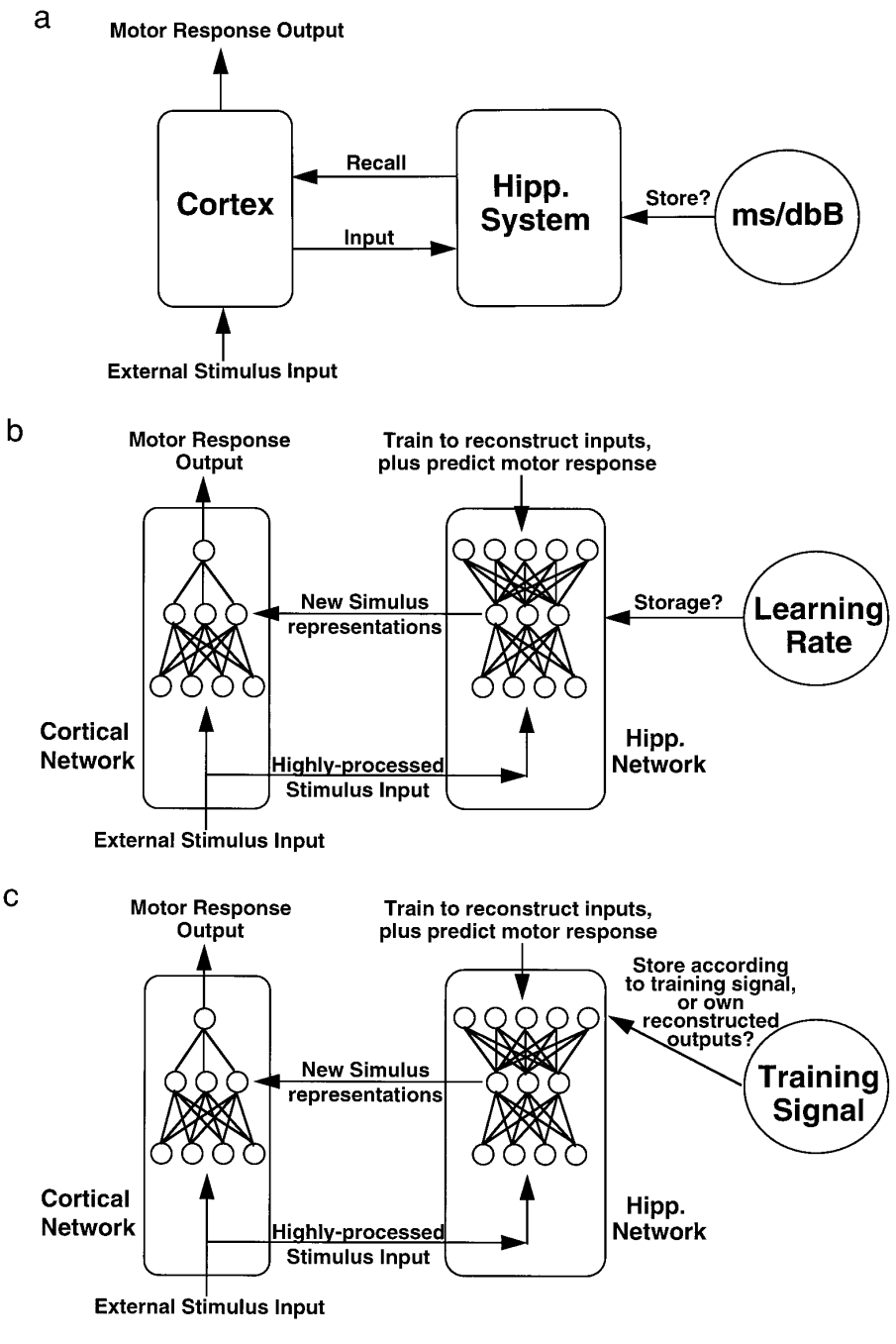

FIG. 6. (A) Highly simplified representation of cortical, hippocampal, and septal interaction, combining the accounts of Gluck and Myers (1993) and Hasselmo and Schnell (1994). The cortex learns and stores mappings between stimulus inputs and behavioral responses; this learning is mediated by (but not necessarily dependent on) the hippocampal region. The medial septum is assumed to determine whether the hippocampal system operates to *store* new information or *recall* stored information and transfer it to cortex. (B) One approach to implementing the processes shown in (A). Medial septal input is assumed to determine hippocampal learning rate, which in turn determines whether the hippocampal network is more prone to store new information or recall stored information. (C) An alternate approach to implementing (A): Medial septal lesion is assumed to degrade the training (storage) in the hippocampal network by allowing intrusion of information from the output (recall) of the hippocampal network. This is formally equivalent to the learning rate manipulation of (B).

patterns as degraded versions of a stored pattern, and to try to reconstruct that stored pattern (e.g., Anderson, 1977). Degrading the hippocampal network training signal, by corrupting it with its own reconstructed outputs, therefore makes the network less responsive to external stimuli and more respon-

sive to its own internally stored information. Figure 6C schematizes this implementation. This also corresponds to altering the storage/recall tradeoff in the manner hypothesized by Hasselmo to result after septal disruption. Mathematically, this is formally the same manipulation as lowering the learning rate; Appendix II shows a formal proof.

The effects of lowering the learning rate on acquisition of a simple conditioned response in the model are shown in Fig. 7A. The curves for lower learning rates have the same overall shape, but are shifted to the right, indicating delayed learning; this is qualitatively the same effect as seen in rabbits after septohippocampal disruption via scopolamine (Fig. 7B). This is to be expected from the structure of the corticohippocampal model. The cortical network can only learn the correct response when its internal representation of the stimulus is no longer changing. This will happen when the hippocampal network has learned to reliably reconstruct the input pattern. After this, the cortical network will learn quickly, at a rate which is not dependent on the hippocampal learning rate. The amount by which learning is slowed in the model is also dependent on the rate of disruption, as summarized in Fig. 7C. The same dose-dependent effect is seen in normal humans under scopolamine, as shown in Fig. 7D (Solomon et al., 1993).

It is interesting to note the relationship between this model of septohippocampal modulation during conditioning and the two-stage conditioning model offered by Prokasy (1972). Prokasy proposed that a period during which the behavioral response was adapted toward its asymptote was preceded by a prior stage in which the response remained relatively constant at its baseline level. Both the absolute baseline level and the temporal duration of this first stage were assumed to vary with individuals. Prokasy's model therefore also predicts the S-shaped acquisition curve shown by the control animals in Fig. 7B. This two-stage model is consistent with the corticohippocampal model; the corticohippocampal model assumes that the hippocampal network forms stimulus representations which are then acquired by the cortical network. The cortical network cannot solve the task until these hippocampal-mediated representations are formed and transferred. Therefore, Fig. 7A shows an initial period of baseline responding before performance improves. The functional consequence of equating cholinergic suppression with a decrease in our hippocampal network's learning rate is, thus, analogous to extending just the first stage of learning within Prokasy's two-stage model. This is consistent with an earlier proposal by Thompson, Berger, Berry, Hoehler, Kettner, and Weisz (1980) that medial septal lesion results in an extension of Prokasy's first stage of learning.

CLINICAL IMPLICATIONS REGARDING CHOLINERGIC THERAPY IN NORMAL AND SEPTAL-LESIONED SUBJECTS

If, as this modeling work suggests, the effect of scopolamine is to reduce acetylcholine and thereby reduce hippocampal storage, administration of cholinergic agonists should largely reverse this effect. This is indeed the case: scopolamine-induced learning deficits can generally be reversed by the cholinergic agonist oxotremorine, the cholinesterase inhibitor physostigmine or related compounds (e.g., Rupniak, Samson, Tye, Field, & Iverson, 1991; Lamberty & Gower, 1991; Iijima, Greig, Garofalo, Spangler, Heller, & Brossi, 1993). Similarly, in subjects with chronically reduced acetylcholine, such as through basal forebrain damage, cholinergic therapy should have an ameliorating effect. This is also the case: Physostigmine can reduce the learning deficits in animals with basal forebrain lesions (Murray & Fibiger, 1985) and has been shown to produce limited, temporary memory improvements in a human subject with discrete basal forebrain damage (Chatterjee, Morris, Bowers, Williamson, Doty, & Heilman, 1993). Patients with Alzheimer's dementia, which typically involves basal forebrain damage and decreased brain acetylcholine levels (Whitehouse, Price, Struble, Clark, Coyle, & DeLong, 1982; Kesner, 1988), also show impairments in learning and memory (de Leon, Golomb, George, Convit, Rusinek, Morys, Bobinski, de Santi, Tarshish, Narkiewicz, & Wisniewski, 1993) which can be ameliorated by physostigmine (Thal, Fuld, Masur, & Sharpless, 1983; Davis & Mohs, 1982; Sevush, Guterman, & Villalon, 1991) or the cholinergic agonist Tacrine (Knapp, Knopman, Solomon, Pendlebury, Davis, & Gracon, 1994; Manning, 1994; Wagstaff & McTavish, 1994). Presumably, cholinergic therapy is effective in these patients by restoring neuropathologically depressed brain ACh levels.

In normals, cholinergic therapy can also produce robust improvements in learning. For example, moderate doses of physostigmine can improve learning in rats (Santucci, Kanof, & Haroutunian, 1989; Sansone, Castellano, Palazzesi, Battaglia, & Ammassari-Teule, 1993) and monkeys (Bartus & Uehara, 1979; Ogura & Aigner, 1993). The cholinergic agonist oxotremine, injected into medial septum, results in facilitated avoidance learning in normal rats (Izquierdo et al., 1992), while the acetylcholinesterase

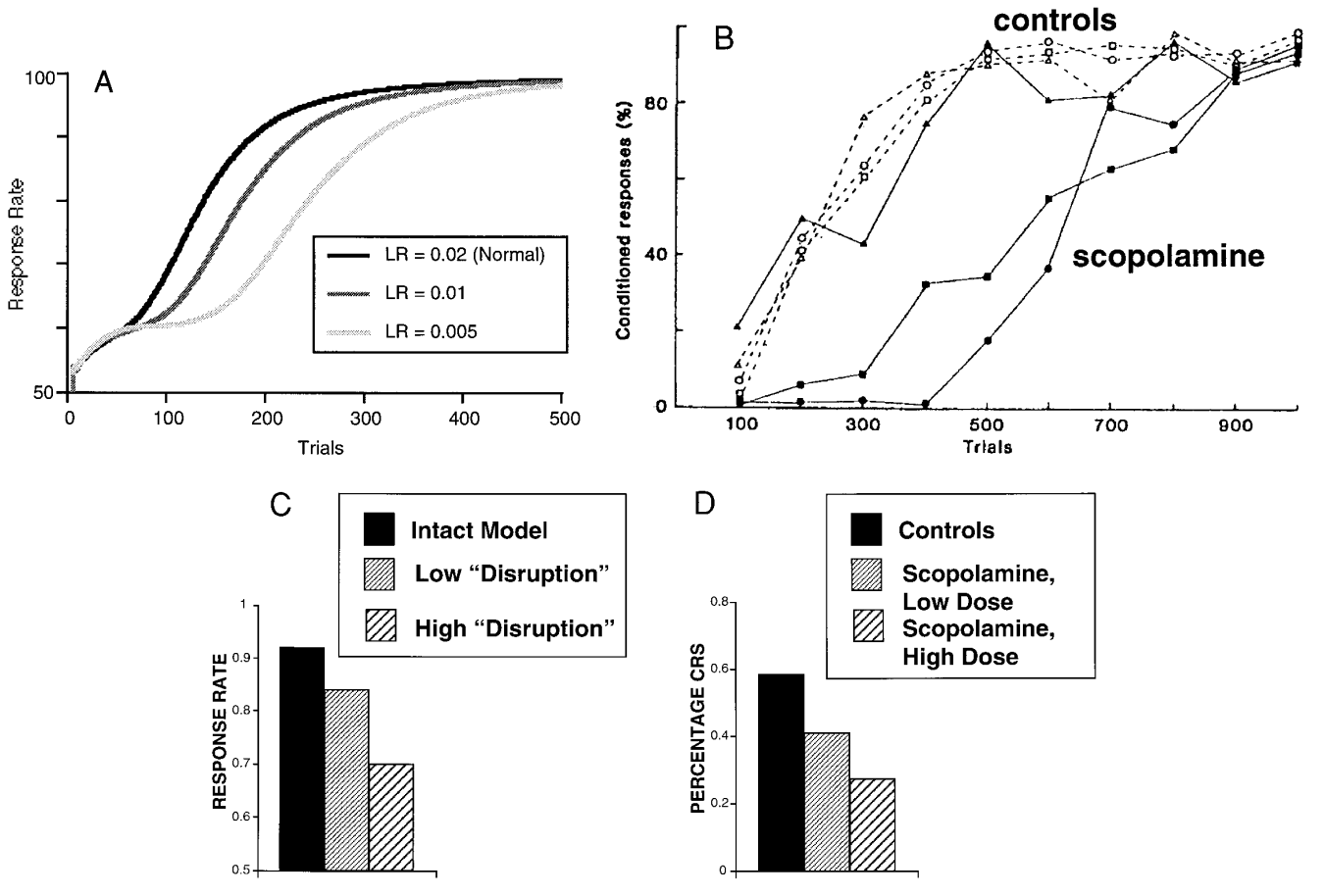

FIG. 7. (A) Learning curves for three different hippocampal learning rates in the model; lowered learning rates shift the acquisition curve right—delaying the onset of learning. (B) For comparison, the rabbit data show a similar delay of conditioning with scopolamine (adapted from Solomon et al., 1983). (C) Model data, replotted to show percent responding after 200 training trials. (D) Human data show a similar dose-dependent effect of scopolamine (after Solomon et al., 1993).

inhibitor galanthamine can improve passive avoidance and water maze learning in normal rats (Sweeney, Bachman, & Coyle, 1990). The effects of such cholinergic drugs can be simulated in the model by raising the hippocampal learning rate, just as the anticholinergic drug scopolamine is presumed to lower it. Figure 8 shows that, to a limited extent, raising the learning rate can improve learning in the model, consistent with the behavioral data.

However, Fig. 8 also shows that raising the hippocampal learning rate beyond some optimal level (about 0.1 for this simulation) actually retards learning in the model. This is a general property of connectionist networks (cf. Jacobs, 1988). This suggests that, while cholinergic agonists may improve learning in subjects with artificially depressed brain acetylcholine, there may be little to gain from cholinergic therapy in normal subjects—and in fact too much hippocampal acetylcholine could actually degrade learning.

In fact, it is the case that cholinergic drugs typically facilitate learning in normal subjects only within a limited dosage range, and dosages exceeding this optimum may either eliminate the facilitation (e.g., Santucci et al., 1989; Ogura & Aigner, 1993; Sweeney et al., 1990; Bartus, 1979; Sansone et al., 1993; Markowska, Olton, & Givens, 1995) or even impair learning (e.g., Ennaceur & Meliani, 1992; Miyamoto, Narumi, Nagaoka, & Coyle, 1989; Dumery, Derer, & Blozovski, 1988). Thus, studies which consider a range of dosages often produce an inverted U-shaped curve: with memory improvements for the optimal dosages and decreased performances for higher dosages. This phenomenon is accounted for in the model as an upsetting of a critical balance between storage and recall. Thus, while too little acetylcholine (as with scopolamine) can upset this balance and impair learning, too much acetylcholine (as with large doses of cholinergic drugs) can impair learning as well. The model therefore pro-

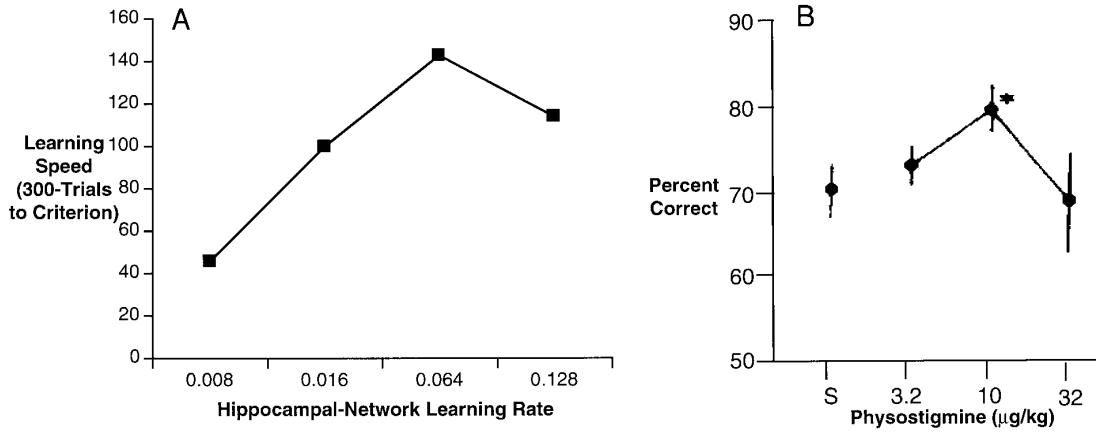

FIG. 8. (A) Speed of learning in the corticohippocampal model (graphed as 300− trials to reach criterion) is a function of the hippocampal-network learning rate. Learning can be degraded by lowering the learning rate from a "normal" level near 0.02 to a "low" level near 0.08; this is presumed to be analogous to the administration of anticholinergics which also retard learning (refer Fig. 7). Increasing the learning rate, e.g., to 0.064, can result in improved learning, presumably similar to the effects of cholinergic agonists. However, beyond some optimum level, further increases (e.g., to 0.126) do not improve learning, predicting that cholinergic drugs will be beneficial only over some limited dosage. Further learning rate increases (e.g., to 0.256) actually result in impaired learning (not shown). (B) A similar dose-dependent effect of physostigmine is often seen in the empirical data. For example, normal monkeys performing a delayed non-matching to sample task show improvement with moderate (10 μg/kg) doses of physostigmine but not with higher (32 μg/kg) doses, compared with controls given saline (S). Figure adapted from Ogura and Aigner, 1993). In other studies, high dosages of physostigmine can actually impair learning (e.g., Ennaceur & Meliani, 1992; Miyamoto, Narumi, Nagaoka, & Coyle, 1989; Dumery, Derer, & Blozovski, 1988).

vides an account of this empirical phenomenon, which has remained problematic in the clinical pharmacology literature.

CONCLUSIONS

In this paper, Hasselmo's theory of septohippocampal modulation during learning (Hasselmo & Schnell, 1994) has been incorporated into Gluck and Myers's (1993) model of corticohippocampal interaction during associative learning, resulting in a more complete model of hippocampal-region function. Specifically, the hippocampal region is assumed to construct new stimulus representations during learning and provide these to cortical areas for long-term storage; the medial septum is assumed to mediate the relative time the hippocampus spends storing new information itself vs. recalling that information and transferring it to cortical stores. The postulated septohippocampal modulation is incorporated into the corticohippocampal model by the simple mechanism of adjusting learning rate in the hippocampal network, but not the rate at which information is transferred to cortex. The resulting model correctly accounts for data from the eyeblink conditioning paradigm, notably that while direct hippocampal lesion does not particularly disrupt simple conditioning, septal lesion can have a devastating effect. Additionally, the model correctly generates a graded learning deficit with increasing levels of septal disruption; this is consistent with data showing that the drug scopolamine, which interrupts cholinergic septohippocampal processes, produces a dose-dependent degradation of conditioning. The model further expects that cholinergic agonists may improve memory, particularly in subjects with preexisting artificial lowering of brain acetylcholine. This is consistent with the known memory improvement after administration of cholinergic drugs in normals and subjects with basal forebrain damage. However, the model expects that cholinergic therapy may only be beneficial to normal subjects in a very limited range; too much acetylcholine will degrade memory. This is consistent with the fact that cholinergic memory drugs are typically only effective for a limited dosage; beyond this dosage, memory may be unaffected or even impaired. This is one example of how computational approaches to neuroscience can help provide a theoretical framework for understanding empirical findings.

In addition to the cholinergic septohippocampal processes, the medial septum also sends other processes to the hippocampus, notably a GABAergic projection (Freund & Antal, 1988; Brazhnik, Vinogradova, Stafekhina, & Kitchigina, 1993b) which may allow the hippocampus to switch between theta and nontheta states, as noted above. Buzsaki (1989) has suggested that the hippocampus enters a "stor-

age" phase during theta states and a "consolidation" phase during nontheta states, during which stored information is gradually transferred to cortex. This septal-mediated consolidation of information from hippocampus to cortex would require that stored representations in the hippocampus should be reinstated, which is just the septal-mediated recall function Hasselmo proposes. Thus, the cholinergic and GABAergic septohippocampal inputs may interact and provide complementary functions. Although anticholinergic drugs such as scopolamine are expected to disrupt septohippocampal cholinergic processes, they might have little direct effect on a GABA-mediated schedule of consolidation. As a result, septal lesion, which disrupts all septohippocampal connections, might be expected to have a more severe effect on learning than anticholinergic drugs; in fact, this appears to be the case (compare Figs. 5A and 5B), but this question remains to be directly tested. Currently, our model cannot shed much light on this issue, as it does not include any account of the GABAergic connections from septum to hippocampus and therefore cannot fully simulate medial septal lesion, only disruption of septohippocampal cholinergic processes.

We note, however, that another computational model of hippocampal function has concentrated on the GABAergic projections from septum to hippocampus (Schmajuk & DiCarlo, 1992). This model assumes that the hippocampus is involved in computing the aggregate prediction of ongoing events and in computing and providing error signals to cerebellum during learning. Hippocampal lesion, in this model, interferes with these processes, allowing only individual associations between stimuli and USs; associations formed prior to the lesion are assumed to be spared. This model and its successors have been fairly successful in accounting for the behaviors of intact and hippocampal-lesioned animals (Schmajuk & DiCarlo, 1992; Schmajuk & Blair, 1993). Within their framework, medial septal GABAergic processes are assumed to modulate hippocampal performance by providing information regarding the error between the actual US and the hippocampal prediction of US. Medial septal lesion is, thus, presumed to disrupt this error signal, interfering with the ability of the hippocampus to provide error information to the cortex. The result is a global decrease in conditioning speed, similar to that shown in the empirical data (refer Fig. 5A; Berry & Solomon, 1979). Schmajuk and DiCarlo's model also correctly expects a global decrease in medial septal activity with continued exposure to stimuli (Berger & Thompson, 1978); since the medial septum is assumed to compute error, continued training should reduce this error and hence reduce medial septal activity. Hasselmo's cholinergic account predicts the same effect: since the medial septum is assumed to become active when the hippocampus encounters novel information, repeated exposure should reduce novelty and hence reduce medial septal activity (Hasselmo et al., 1995). An interesting and important future direction is to determine the extent to which septohippocampal GABAergic and cholinergic processes interact and cooperate. Computational models may be able to provide some insights here, by providing a framework for examining theories.

To examine this issue empirically would require studies systematically comparing the effects of anticholinergic drugs such as scopolamine with the effects of basal forebrain damage. In addition to animal models, human studies would be useful. The effects of scopolamine on human eyeblink conditioning are fairly well characterized, as discussed above, so it remains to identify a population with relatively discrete basal forebrain damage, for comparison. Such a population may be found among survivors of anterior communicating artery (ACoA) aneurysm rupture. The ACoA is the small blood vessel that interconnects the left and right anterior cerebral arteries and which gives rise to a variable number of smaller blood vessels which vascularize the basal forebrain structures (Crowell & Morawetz, 1977). ACoA rupture can result in basal forebrain infarction, to a degree dependent on the size and location of the aneurysm and the number and extent of collaterals involved. About 15% of ACoA aneurysm survivors present with a syndrome including dense anterograde amnesia (DeLuca & Diamond, 1994). This amnesia occurs in the absence of direct hippocampal damage but is believed to result from basal forebrain damage (Irle, Woura, Kunert, Hampl, & Kunze, 1992). If so, we would expect these patients to show dramatic disruption in eyeblink conditioning. This would be in stark contrast to the preserved eyeblink conditioning observed in hippocampal-damaged amnesics (refer Fig. 4A). Such a result would begin to address the important question of whether there are different amnesic syndromes, depending on different etiology.

This general computational approach to investigate neuromodulation of hippocampal function may be extensible to other neuromodulators, such as norepinephrine, dopamine, and serotonin. Whereas neurotransmitters function to carry information between brain cells, neuromodulators affect how that information is processed (Hasselmo, 1995). For example, norepinephrine is believed to signal high vigi-

lance to external stimuli and events (Aston-Jones & Bloom, 1981). In the corticohippocampal model, this signal would correspond to short-term adjustments in the hippocampal (and possibly cortical) learning rates during presentation of salient stimuli. Other neuromodulators are similarly important; for example, schizophrenia may partly result from dopamine imbalance in the hippocampus (e.g., Krieckhaus, Donahoe, & Morgan, 1992). Extension of the modeling techniques presented here to account for the roles of these other neuromodulators remains a future line of research.

APPENDIX I: SIMULATION DETAILS

The corticohippocampal model generating the simulation results shown in this article is an adaptation of that described in Gluck and Myers (1993).

The hippocampal network is a fully connected autoencoder (Hinton, 1989) with 19 input nodes, 10 internal-layer nodes, and 19 output nodes. The input to this network is a vector with three elements specifying the presence or absence of up to three CSs, 15 "context" elements each randomly (but fixedly) set to 0.0 or 1.0, and a final element constantly set to 0.0. The desired output for this network is a reproduction of this input vector, with the final element indicating the presence or absence of the US on the current trial. This network is trained by the standard error backpropagation algorithm (Hinton, Rumelhart, & Williams, 1986). Output y_j for each node j is computed via a logistic activation function

$$y_j = f(\sum_i w_{ij} y_i + \theta_j)$$

$$f(x) = \frac{1}{(1 + e^{-x})}.$$

Error signals for the output nodes are calculated by

$$\delta_j = (I_j - y_j) y_j (1 - y_j),$$

where I_j is the training signal and y_j the output for output node j. Error signals are backpropagated to internal nodes by

$$\delta_j = y_j (1 - y_j)(\sum_k w_{jk} \delta_k).$$

Weights are changed by a momentum rule

$$w_{ij} \rightarrow w_{ij} + \Delta w_{ij}$$

$$\Delta w_{ij} \rightarrow \alpha(\Delta w_{ij}) + \beta \delta_j y_i.$$

The learning rate (α) is 0.02, except when adjusted to simulate the effects of cholinergic drugs, and is increased 10-fold on trials where the US is present. Momentum (β) is set at 0.9.

The cortical network is a fully connected feed-forward network, with 18 input nodes, 60 internal-layer nodes, and 1 output node. The inputs are the same as the first 18 elements of the hippocampal network input; the desired output is the presence or absence of the US. Output nodes in this network are trained in the same way as output nodes in the hippocampal network, except that the learning rate is 0.005. Internal-layer nodes j are trained by computing the desired output as the difference between y_j and a weighted sum of the outputs of the internal-layer nodes in the hippocampal network, and then using the weight-change rule described above. The learning rate for the internal layer nodes is 0.001. Again, the learning rate increases 10-fold on US-present trials, and the momentum is 0.9.

All weights and biases in the system are initialized randomly from U(−0.3, 0.3). The full corticohippocampal system is initialized for 200 trials with CS and US absent.

APPENDIX II

Proof of Equivalence of Disrupting Output and Lowering Learning Rate in the Hippocampal Network

The hippocampal network is a fully connected three-layer network, trained by the error backpropagation algorithm (Rumelhart, Hinton, & Williams, 1986) according to the weight-change rule

$$w_{ij} \rightarrow w_{ij} + \Delta w_{ij}$$

$$\Delta w_{ij} \rightarrow \alpha(\Delta w_{ij}) + \beta \delta_j y_i.$$

The effects of scopolamine on the hippocampal region are simulated by a simple lowering of learning rate β. We show here that this is analogous to the proposition of Hasselmo that the effect of reducing acetylcholine is equivalent to making the hippocampus respond less to external stimuli and more to its own internal (recalled) state. In the corticohippocampal model, reducing the effects of external stimuli would correspond to corrupting the desired output I_j of the hippocampal network's output nodes, by including the influence of the actual network output y_j:

$$I'_j = (1 - \sigma) I_j + \sigma y_j,$$

where $0 \leqslant \sigma \leqslant 1$ represents the scopolamine dose. This will change the error for the output nodes to

$$\delta_j' = (1 - \sigma)\delta_j$$

for output nodes, and also for internal nodes, since their error is calculated by backpropagation, which is linear. The weight change will become

$$\Delta w_{ij}' = \beta\delta_j' y_i = \beta(1 - \sigma)\delta_j y_i = \beta'\delta_j y_i,$$

where $\beta' = (1 - \sigma)\beta$. Therefore, since $0 \leqslant \sigma \leqslant 1$, the effect is simply to lower the learning rate.

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