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A Connectionist Model of Septohippocampal Dynamics During Conditioning: Closing the Loop

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Septohippocampal interactions determine how stimuli are encoded during conditioning. This study extends a previous neurocomputational model of corticohippocampal processing to incorporate hippocamposeptal feedback and examines how the presence or absence of such feedback affects learning in the model. The effects of septal modulation in conditioning were simulated by dynamically adjusting the hippocampal learning rate on the basis of how well the hippocampal system encoded stimuli. The model successfully accounts for changes in behavior and septohippocampal activity observed in studies of the acquisition, retention, and generalization of conditioned responses and accounts for the effects of septal disruption on conditioning. The model provides a computational, neurally based synthesis of prior learning theories that predicts changes in medial septal activity based on the novelty of stimulus events.

The septal region modulates a wide range of neurobehavioral processes, including voluntary movements, emotion, attention, and the formation and recollection of memories (for review, see Numan, 2000). Scientists generally agree that the primary role of septal modulation in learning is to control when hippocampal processing leads to the storage of information (Baxter, Gallagher, & Holland, 1999; Buhusi & Schmajuk, 1996; Hasselmo, 1995). When either the septum or septohippocampal connections are damaged, learning is greatly impaired (for review, see Decker, Bannon, & Curzon, 2000). Such deficits are characteristic of neurodegenerative disorders such as Alzheimer's disease that involve septal dysfunction (Menschik & Finkel, 1998). Although septohippocampal interactions clearly play a critical role in information processing, the effect of these interactions on learning is not well understood. Computational models provide a way of quantitatively analyzing how the septohippocampal system might function.

In a previous article, Myers et al. (1996) generalized an existing model of corticohippocampal interaction in associative learning to account for the effects of septohippocampal modulation. In this model, the hippocampal system (including the hippocampus, subiculum, and entorhinal cortex) adaptively modifies stimulus representations to compress redundant information while differentiating predictive information. The model assumes that cortical networks use these hippocampal representations to efficiently recode their stimulus representations (Gluck & Myers, 1993, 2001). This model accounts for a wide range of data on associative learning in normal animals as well as in animals with damaged septohippocampal systems (Myers & Gluck, 1994, 1996; Myers, Gluck, & Granger, 1996). Myers et al. (1996) noted that the role of septal modulation in hippocampal dynamics hypothesized by Hasselmo and colleagues (Hasselmo, 1995; Hasselmo & Schnell, 1994; Hasselmo, Wyble, & Wallenstein, 1996) could be implemented in the Gluck and Myers (1993) corticohippocampal model by assuming that changing the learning rate in the hippocampal system is equivalent to adjusting the amount of time the hippocampus spends storing information. This simple manipulation suffices to account for the effects of septal disruption on the acquisition of a classically conditioned response in humans (Gluck, Allen, & Myers, 2001; Solomon et al., 1993) and other animals (Solomon, Solomon, van der Schaaf, & Perry, 1983) and for the effects of scopolamine on latent inhibition, learned irrelevance, and extinction (Myers, Ermita, Hasselmo, & Gluck, 1998).

Hasselmo and Schnell (1994) suggested that although septohippocampal modulation determines what information is stored and recalled in the hippocampus, neurons in the hippocampal system help determine the dynamics of septal modulation. They proposed that signals sent from hippocampal neurons to the septal region indicate how well stimulus representations are encoded. Thus, the hippocampus self-regulates stimulus encoding through septal feedback. Extensive anatomical and electrophysiological data demonstrate the existence of septohippocamposeptal loops (see Figure 1; reviewed by Denham & Borisyuk, 2000; Dragoi, Carpi, Recce, Csicsvari, & Buzsaki, 1999; Jakab & Leranth, 1995; Leranth & Vertes, 2000; Sheehan & Numan, 2000). Past computational models of septohippocampal processing have often incorporated such loops (Buhusi & Schmajuk, 1996; Denham & Borisyuk, 2000; Hasselmo & Schnell, 1994; Hasselmo & Wyble, 1997; Hasselmo et al., 1996). Nevertheless, the dynamics of self-regulation in the septohippocampal system during learning of new information have not been well specified, and the manner in which changes in septohippocampal dynamics (e.g., induced chemically or through

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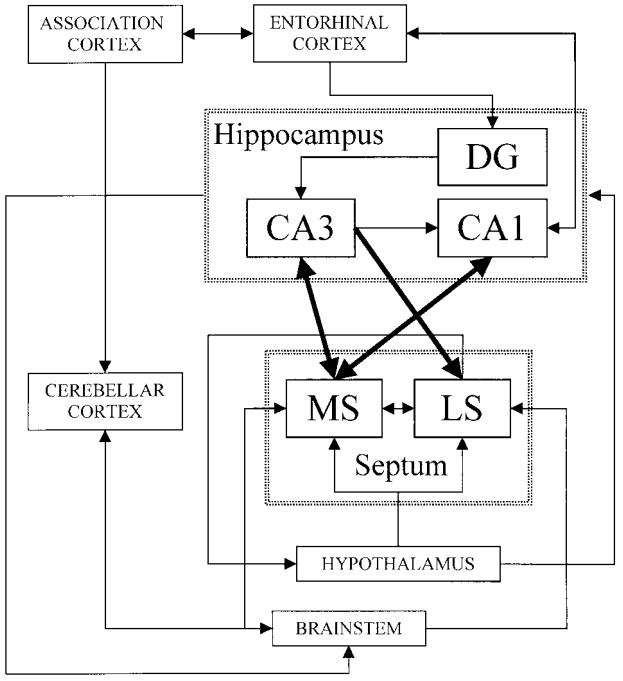

Figure 1. Schematic of information pathways in the septohippocampal system. Sensory information is sent from the association cortex, through the entorhinal cortex, to the hippocampus. Hippocampal neurons project to the septum, entorhinal cortex, and brainstem. Signals from both the association cortex and the brainstem affect cerebellar processing. Septal neurons project to the hippocampus and hypothalamus. Thus, the hippocampus could modulate activity in the medial septum (MS) directly (Gaykema, van der Kuil, Hersh, & Luiten, 1991; Toth, Borhegyi, & Freund, 1993; Toth & Freund, 1992) or indirectly via the lateral septum (LS) and brainstem (Leranth & Frotscher, 1989; Swanson & Cowan, 1979). Similarly, septal neurons could modulate the hippocampus both directly via MS projections (Nauta & Feirtag, 1986) and indirectly through LS projections to the hypothalamus (Jakab & Leranth, 1995; Leranth, Deller, & Buzsaki, 1992). Adapted from Hasselmo (2000), Schmajuk (1997), and Sheehan and Numan (2000). DG = dentate gyrus; CA = cornu ammonis.

physical damage) affect information processing is poorly understood.

In this article, we extend the Myers et al. (1996) computational model of septohippocampal processing in associative conditioning to include the effects of recurrent septohippocamposeptal modulation. The resulting model provides a framework for reexamining septohippocampal dynamics during conditioning as observed in past behavioral and neurophysiological studies. The model characterizes septohippocampal function in a wide range of conditioning tasks and makes novel predictions about septal activity during extinction, discrimination reversal learning, and blocking. We present new experimental data from studies of blocking that are consistent with the predictions of our model.

A Connectionist Model of Septohippocampal Processing

We first review the Gluck and Myers (1993) model of how stimulus representations are encoded by the hippocampal system during associative conditioning and how this theory has been instantiated in a connectionist network model. We then review how septal modulation is implemented within this model.

The Corticohippocampal Model

In Gluck and Myers's (1993) theory of hippocampal processing, stimulus representations correspond to activity patterns across a set of hippocampal neurons that encode inputs. A key assumption of this theory is that highly differentiable stimulus representations are easier to associate with different behavioral responses than are highly similar representations. Differentiation of stimulus representations can thus facilitate the association of stimuli with responses. Gluck and Myers (1993) proposed that the hippocampal system modifies stimulus representations to facilitate associative learning. In particular, they suggested that when stimuli are redundant, then the hippocampal system will recode the representations of these stimuli such that they are more similar. Conversely, when stimuli are predictive of different outcomes, then the hippocampal system will transform the representations of these stimuli into more dissimilar representations.

This theory was instantiated as a connectionist model (see Figure 2), accounting for the role of hippocampal processing in classical conditioning of an eyeblink response. In eyeblink conditioning, a blink-evoking corneal airpuff (the unconditioned stimulus or US) is repeatedly paired with presentation of a sensory stimulus (the conditioned stimulus or CS). After repeated pairings,

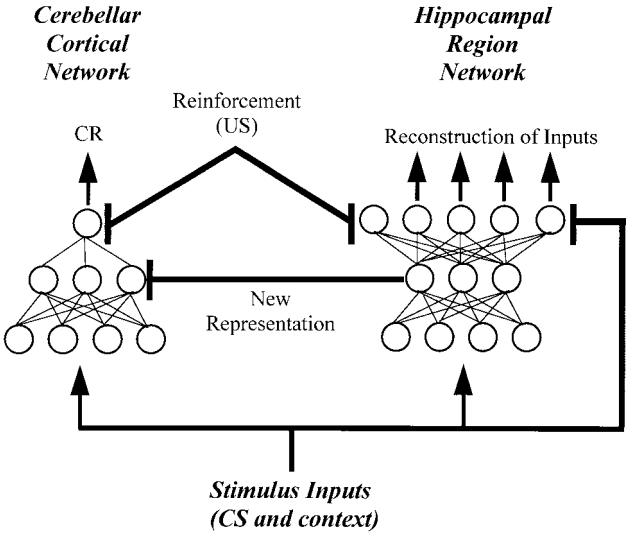

Figure 2. The corticohippocampal model (Gluck & Myers, 1993). The cerebellar cortical network on the left (a multilayer perceptron) learns to map from its inputs to an internal representation provided by the hippocampal region network on the right (a predictive autoencoder) and from those representations to an output that determines the probability of a conditioned response (CR). The strength of this response also serves as a measure of how well the hippocampal network predicts the unconditioned stimulus (US). The hippocampal region network learns to predict the US and reconstruct stimulus inputs while forming new stimulus representations in its internal layer that differentiate predictive information and compress redundant information. Arrows represent inputs and outputs, circles represent nodes (computational units), and bars indicate transmittal of desired states used to train networks. CS = conditioned stimulus.

the subject acquires an association between the CS and the US, such that presentation of the CS alone can elicit an anticipatory eyeblink response (Berger & Thompson, 1978). This preparation has been used to study learning in several species, such as humans (Solomon et al., 1993), rabbits (R. F. Thompson, 1986, 1990), and rats (Schmajuk, Lam, & Christiansen, 1994).

Whereas cerebellar processing is necessary for the acquisition of a conditioned eyeblink response (reviewed by R. Thompson et al., 1997), hippocampal processing is not (Daum, Channon, & Canavan, 1989; Gabrieli et al., 1995; Port & Patterson, 1984; Schmajuk et al., 1994; Schmaltz & Theios, 1972; Weiskrantz & Warrington, 1979; Woodruff-Pak, 1993). Eyeblink conditioning is affected by hippocampal region damage, however, when relatively complex temporal and correlational relationships exist between conditioned and unconditioned stimuli (Moyer, Deyo, & Disterhoft, 1990; Solomon & Moore, 1975). Physiological, pharmacological, and behavioral data suggest that during classical conditioning, both neutral conditioned stimuli and noxious unconditioned stimuli are encoded in the hippocampal system before being transferred to long-term memory (for review, see Sears & Steinmetz, 1990). Conditioned and unconditioned stimuli normally evoke activity in the hippocampus (Berger & Thompson, 1977, 1978). Gluck and Myers (1993) interpreted these results as evidence that the cerebellar cortex uses hippocampal representations to recode its own stimulus representations. When hippocampal representations are not available, the cerebellum is less able to form certain types of stimulus–response associations.

Gluck and Myers (1993) modeled the hippocampal system as a predictive autoencoder (Baldi & Hornik, 1989; Hinton, 1989) and the cerebellar cortex as a multilayer perceptron (Rumelhart, Hinton, & Williams, 1986) (see Figure 2). The autoencoder network learns to reconstruct input representations (corresponding to sensory stimuli) and to predict the occurrence of a second input (corresponding to a US), through a narrow internal node layer. The internal layer of this network contains fewer nodes than either the input or output layers, such that the autoencoder is forced to compress redundant properties of stimulus representations, while preserving and differentiating properties that predict the presence or absence of a US.

The cerebellar cortical network learns to map from inputs (corresponding to sensory stimuli) to a pattern of activations in an internal layer of nodes, which is then mapped to an output node representing the behavioral response. This network cannot form new representations in its internal layer. It can, however, adopt the representations formed in the internal layer of the hippocampal network (or linear transformations of these representations) and map them onto behavioral responses (for simulation details, see Gluck & Myers, 1993). When the hippocampal network is not present, the patterns of activation in the internal layer of the cerebellar network become fixed.

The Gluck and Myers (1993) corticohippocampal model provides a simple and unified interpretation of the trial-level effects of hippocampal lesions on classical conditioning, contextual learning (Myers & Gluck, 1994), probabilistic category learning (Gluck, Oliver, & Myers, 1996), and discrimination learning (Myers & Gluck, 1996).

Septohippocampal Modulation

The components of the hippocampal system discussed so far center on the hippocampal region and how it affects cerebellar cortical processing. The hippocampus has other connections, however, including modulatory inputs from surrounding limbic structures. One such structure, the medial septum, strongly modulates hippocampal activity (Buzsaki & Eidelberg, 1983; Hasselmo, 1995; Nauta & Feirtag, 1986; Nolte, 1993). Medial septal neurons project to the hippocampus via the fornix. Neuromodulatory chemicals released from these projections (in particular, acetylcholine and gamma-aminobutyric acid [GABA]) strongly affect patterns of neural activity in the hippocampal system (Berry, Seager, Asaka, & Griffin, 2001; Hasselmo & Schnell, 1994).

Medial septal lesions greatly retard acquisition of eyeblink conditioning (Berry & Thompson, 1979; Ermita, Allen, Gluck, & Zaborszky, 1999). Similarly, pharmacological disruption of the medial septum (e.g., through injection of the muscarinic cholinergic antagonist scopolamine) impairs conditioning in rabbits (Asaka, Seager, Griffin, & Berry, 2000; Solomon et al., 1983) and humans (Solomon et al., 1993). Thus, disrupting hippocampal function by manipulating septal modulation can impair conditioning to a greater extent than removing the hippocampus (Solomon et al., 1983). Conversely, septal modulation can enhance pyramidal cell excitability in the hippocampus by suppressing adaptation (Barkai & Hasselmo, 1994; Madison, Lancaster, & Nicoll, 1987) and enhancing synaptic plasticity (Hasselmo & Barkai, 1995; Huerta & Lisman, 1993).

Myers et al. (1996) argued that the effect of septal disruption by scopolamine was to slow down hippocampal encoding of stimulus representations. They instantiated this idea in the corticohippocampal model by decreasing the learning rate of the autoencoder network. With this manipulation, the model accounts for the effects of scopolamine on classical conditioning in a wide variety of preparations (Myers et al., 1998). The model also accounts for the finding of a U-shaped dose–response curve for cholinergic agonists in normal subjects (Myers et al., 1996).

Modeling Hippocamposeptal Feedback Effects

Septal activity may be regulated by how successfully the hippocampal system encodes stimulus representations (Hasselmo & Schnell, 1994). In the following sections, we describe how hippocampal encoding might drive medial septal activity and how the existing corticohippocampal model can be modified to incorporate this aspect of hippocampal processing.

Novelty Detection

Performance in classical conditioning tasks is dependent on stimulus novelty. For example, conditioning of a response is quicker when a novel stimulus is used, compared with when an already familiar stimulus is used, an effect known as *latent inhibition* (Lubow, 1973). Activity in the medial septum is also dependent on novelty. Neurons in the medial septum respond strongly when novel, but not familiar, stimuli are presented (Berger & Thompson, 1977). Such changes may be mediated in part by the hippocampal system, which is thought to play an important role in novelty detection (e.g., see Borisyuk, Denham,

Hoppensteadt, Kazanovich, & Vinogradova, 2001; Givens, Williams, & Gill, 2000; Honey, Watt, & Good, 1998). Together, these findings suggest that the effects of novelty (or familiarity) on conditioning are mediated by septohippocampal processing.

In the Gluck and Myers (1993) model, familiar stimuli are generally encoded more successfully in the hippocampal network than are novel stimuli. By learning to encode and reconstruct inputs, the hippocampal network becomes very effective at detecting novel inputs based on differences in encoding–reconstruction errors (Japkowicz, 1999; Japkowicz, Myers, & Gluck, 1995). Similar recognition-based novelty detection may be performed by the hippocampal system. For example, Hasselmo and Wyble (1997) suggested that hippocampal subfield CA3 reconstructs inputs from the entorhinal cortex and that hippocampal subfield CA1 then compares the inputs from the entorhinal cortex with the reconstructed outputs from CA3. When stimuli are well encoded, the patterns in the entorhinal cortex and CA3 will be similar, and CA1 neurons will inhibit activity in the medial septum. When stimuli are novel and encoding is poor, CA1 will release the medial septum from inhibition. Thus, a novel stimulus initially elevates septal activity, increasing the rate of hippocampal encoding. With repeated presentation, encoding of stimuli becomes more accurate. Septal activity gradually diminishes as the accuracy of encoding increases, reducing the rate of hippocampal encoding (see Figure 3).

We assume that during conditioning, the septohippocampal system continuously assesses whether existing stimulus representations are sufficiently differentiatied to distinguish stimuli that do or do not predict the arrival of a noxious stimulus (see also Green & Woodruff-Pak, 2000). The hippocampal system reacts to poorly encoded stimuli (e.g., novel stimuli) by increasing septal activity, thereby increasing the rate of hippocampal encoding (as proposed by Hasselmo & Wyble, 1997). Stimulus representations continue to be modified until it is possible for stimuli that signal the arrival of a noxious stimulus to be distinguished from other, nonpredictive stimuli. The better the septohippocampal system can recognize relevant relationships between stimuli (e.g., a predictive association between a tone and an airpuff), the more septal activity will be inhibited.

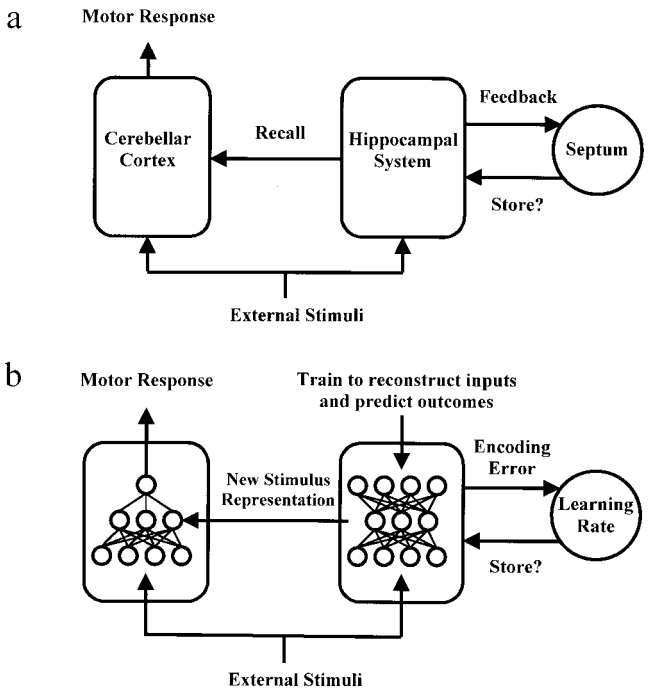

Figure 3. a: Highly simplified schematic of cerebellar, hippocampal, and septal interactions. The cerebellar cortex learns and stores mappings between external stimuli (corresponding to thalamocortical inputs) and motor responses; this learning is mediated by, but not necessarily dependent on, hippocampal processing. Septal modulation is assumed to control whether the hippocampal system stores new information or recalls previously stored information. Feedback from the hippocampal system is hypothesized to self-regulate this process (Myers et al., 1996). b: Medial septal input is assumed to control learning rate in the hippocampal network. Learning rate affects how rapidly stimulus representations are encoded in the hippocampal network, which in turn affects the accuracy of stimulus reconstruction and prediction of outcomes (measured by means of encoding error). Higher encoding errors lead to higher learning rates, which lead to larger changes in stimulus representations. Arrows represent the flow of information; circles represent modulatory systems.

Simulating Septohippocampal Interactions

To examine how hippocamposeptal feedback might affect the role of hippocampal processing in conditioning, we compared performance of an expanded corticohippocampal model, in which learning rate depended on hippocampal encoding error (simulating active feedback modulation), with performance of the original corticohippocampal model, in which learning rate was fixed (simulating modulatory effects that are independent of hippocampal activity or stimulus novelty). We subsequently refer to these two models as the *dynamic model* and the *static model*, respectively.

Implementation details of the basic corticohippocampal model have been described previously (Gluck & Myers, 1993; Myers et al., 1996); we thus only present details specific to the simulations described in this article. The hippocampal component of the network (the fully connected, predictive autoencoder depicted in Figure 2) consisted of 15 input nodes, 8 hidden nodes, and 16 output nodes. The cerebellar network (the fully connected multilayer perceptron shown in Figure 2) consisted of 15 input nodes, 40 hidden nodes, and 1 output node. Both networks received inputs corresponding to conditioned stimuli (orthogonal binary strings of length 5) and contextual stimuli (random binary strings of length 10). The 16 output nodes in the hippocampal network correspond to the 15 input nodes plus an additional node encoding the presence or absence of the US.

Training in the hippocampal network was performed using a standard error back-propagation algorithm (Rumelhart et al., 1986), whereas training in the cerebellar network was performed using a least mean square algorithm (Widrow & Hoff, 1960). Learning rate for the cerebellar network was fixed at 0.5 for output nodes and 0.1 for internal layer nodes for all simulations. In the static model, learning rate for the hippocampal network was fixed at 0.05. Learning rate in the dynamic model was calculated by multiplying the standard learning rate parameter by a modulation factor. This modulation factor was calculated (in the form of a Hamming distance metric) on the basis of the sum of the absolute difference between each input node and its accompanying output node, plus the absolute difference between the predicted US and

the actual US. Encoding error (and consequently, learning rate) thus increased when the hippocampal network failed to reconstruct the input pattern or to predict the US. (Details of the dynamic learning algorithm used in this model are provided in Rokers, Myers, & Gluck, 2000.) The model assumes that if hippocampo-septal feedback is blocked (either chemically or through physical damage), learning rate in the system is no longer affected by hippocampal encoding.

In each simulation, the corticohippocampal network was initialized by training it with 200 context-alone trials, followed by 200 conditioning trials. Effectiveness of conditioning in the corticohippocampal model was assessed on the basis of the probability that a CS would elicit a conditioned response (CR) after training (the criterion probability for successful conditioning was defined to be 0.8). The modulation factor in the dynamic model provided a global measure of encoding error in the hippocampal network and was thus used as a measure of medial septal activity. Simulations with the static model were equivalent to those with the dynamic model, except that there was no modulation of learning rate based on encoding error. For all simulations discussed, results were averaged over five simulation runs.

Both the static and dynamic models generate predictions about how septal activity levels affect behavioral responses during classical conditioning. In the following sections, we compare our simulation results with available experimental data on septal activity and CRs observed during various conditioning procedures.

Septohippocampal Dynamics During Conditioning

Behavior and Septal Activity During Acquisition

Neural activity in the medial and lateral septum changes across trials as an animal learns to make a conditioned eyeblink response (Berger & Thompson, 1978; Miller & Steinmetz, 1992). Changes in lateral septum activity usually parallel changes in hippocampal activity. For example, during early phases of training, activity levels in the hippocampus and lateral septum are high immediately after the onset of a US. A CS that predicts the onset of a US will not initially evoke increased activity in the hippocampus or lateral septum. As training progresses, however, changes in evoked activity are often observed to occur earlier in the interval between CS presentation and US onset, until eventually increased activity coincides with CS onset in both the lateral septum and hippocampus. In contrast, presentations of both conditioned and unconditioned stimuli evoke activity in the medial septum early in training. Levels of evoked medial septal activity decrease over the course of training, whereas levels of lateral septum and hippocampal activity remain approximately constant. CS-evoked lateral septum activity (which corresponds closely with production of a behavioral response) rises sharply only after medial septal activity has reached a plateau, suggesting that acquisition of a CR typically occurs after an increase in medial septal activity. These conditioning-induced changes in CS-evoked septal activity are summarized in Figure 4a. Differences in the responses of neurons in the lateral and medial septum suggest that these two groups of neurons serve separate functions (Zhou, Tamura, Kuriwaki, & Ono, 1999).

The static corticohippocampal model uses a fixed learning rate, and thus septal modulation levels are constant during conditioning (Myers et al., 1996, 1998). In the dynamic model, learning rate in the hippocampal network (simulating activity levels in the medial septum) varies as a function of encoding error. Because CS-evoked activity in the lateral septum corresponds closely to production of a CR, we use the CR generated by the cortical network as an estimate of lateral septal activity to compare our simulation results with electrophysiological data.

The dynamic model exhibits a similar pattern of activity during conditioning to that observed experimentally (see Figure 4b). Medial septal activity decreases as a function of training, whereas the probability of a CR increases steadily. Medial septal activity does not rise immediately at the onset of training, but rises sharply to peak shortly before Trial 20. This result occurs because the increased modulation levels initially lead to disruption of representations in the hippocampal network formed during context-only conditioning, generating encoding errors for contextual patterns that previously did not elevate modulation levels. The feedback signal reflects how poorly the CS is encoded and how poorly the CS predicts the US. Increased medial septal activity does not directly influence acquisition of the CR, but rather drives the hippocampus into a learning state, which leads to reorganization of stimulus representations, thereby increasing the ability of the cortical network to discriminate between stimuli that are predictive of the US and stimuli that are not. As a result, the dynamic model learns to produce CRs more rapidly than the static model (see Figure 5).

Changes in medial septal activity (as indicated by changes in acetylcholine levels in the hippocampus) have also been observed during acquisition of a positively reinforced operant conditioning task. Orsetti, Casamenti, and Pepeu (1996) used microdialysis techniques to measure changes in hippocampal cholinergic levels while rats learned to press a lever for a food reward. Rats were trained in a sound-isolated chamber equipped with a single lever; the total number of responses and acetylcholine levels were recorded every 30 min. Orsetti and colleagues observed that large increases in responding were preceded by increases in hippocampal cholinergic levels (see Figure 6). Once the rats reached a stable rate of leverpressing, cholinergic levels returned to preconditioning levels. These findings can be interpreted within the framework of the dynamic corticohippocampal model. When contextual and conditioned stimuli that lead to leverpresses begin to be encoded, this leads to increased medial septal activity, which in turn increases cholinergic levels in the hippocampus. As representations of these stimuli become more efficiently encoded, medial septal activity (and cholinergic levels) decrease, whereas responding increases (as illustrated in Figure 4b). The dynamic corticohippocampal model shows a more gradual decrease in medial septal activity over time than is evidenced by the changes in hippocampal cholinergic levels reported by Orsetti and colleagues. They note, however, that long collection times may have masked short-lasting changes. The dynamic model predicts that if measurements had been made during each leverpress occurring after the 2nd hr of training in Orsetti et al.'s experiment, then a more gradual decrease in cholinergic levels would have been observed.

Behavior and Septal Activity During Extinction and Reacquisition

After eyeblink conditioning, if the CS is repeatedly presented in the absence of the US, responding to the CS eventually extin-

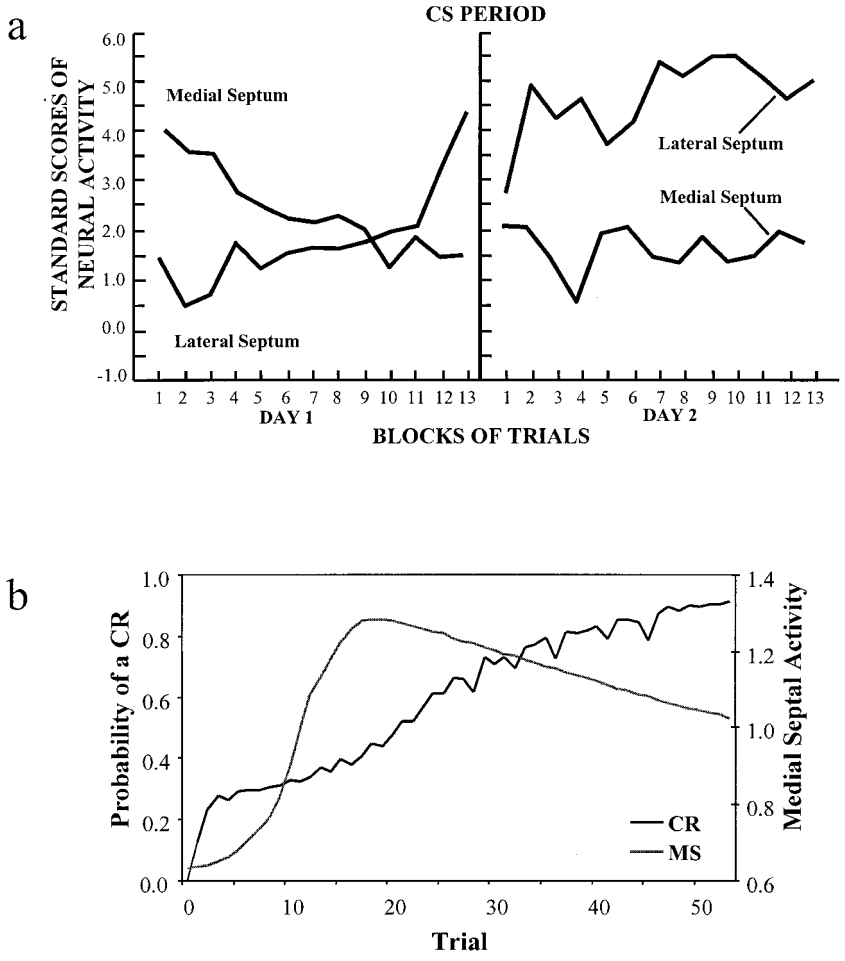

Figure 4. Increased medial septal (MS) activity precedes increased lateral septal activity and acquisition of a classically conditioned response (CR) in empirical tests and in simulations with the dynamic corticohippocampal model. a: Septal activity (in arbitrary units) during acquisition of a classically conditioned eyeblink response. Reprinted from *Brain Research, 156,* T. W. Berger and R. F. Thompson, "Neuronal Plasticity in the Limbic System During Classical Conditioning of the Rabbit Nictitating Membrane Response: II. Septum and Mamillary Bodies," pp. 293–314, Copyright 1978, with permission from Excerpta Media, Inc. b: Simulated MS activity and conditioned responding in the dynamic corticohippocampal model. CS = conditioned stimulus.

guishes. Both the static and the dynamic corticohippocampal models predict that medial septal activity levels should remain stable (and low) as a CR is extinguished and that disruption of hippocamposeptal feedback should not affect the rate of extinction.

If, after extinction, the CS is again paired with the US, the CR will be acquired much faster than previously (e.g., Robbins, 1990). Similar cases of rapid reacquisition have also been observed in operant conditioning tasks (Orsetti et al., 1996). Cholinergic levels in the hippocampus do not increase during reacquisition of an extinguished response, suggesting that medial septal activity is stable during reacquisition (see Figure 7a; adapted from Orsetti et al., 1996). Similarly, in the dynamic corticohippocampal model (Figure 7b), medial septal activity does not change during reacquisition of an extinguished response. Learning rate is stable because existing stimulus representations of the CS acquired during previous training are still available (i.e., stimulus representations in the hippocampal and cerebellar cortical network are stable until they need to be made more or less discriminable).

Behavior and Septal Activity During Multiple-Phase Learning

Past modeling work by Gluck and Myers (1993) suggests that hippocampal region damage should not impair conditioned eyeblink responding unless new stimulus representations are required. However, representations of conditioned stimuli in intact animals should differ from those in animals with hippocampal damage, after training. Such differences are most likely to be evident in tasks that involve secondary tests of transfer or generalization of learned associations. Multiple-phase conditioning tasks can thus be particularly useful for investigating the role of septohippocampal processing in conditioning.

Discrimination Reversal

Reversal learning tasks involve at least two phases of training. In the first phase, CS1 is associated with a US, whereas a second

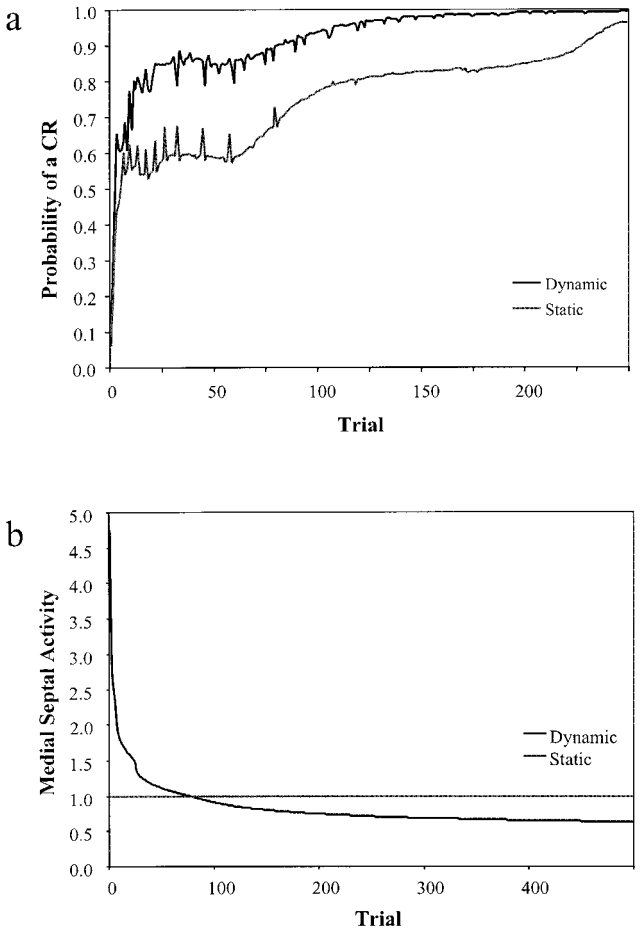

Figure 5. Acquisition is more rapid in the dynamic corticohippocampal model than in the static model (a), although medial septal activity (i.e., learning rate, in arbitrary units) is lower, on average, in the dynamic model (b). CR = conditioned response.

CS (CS2) is presented an equal number of times in the absence of any US. After subjects have learned that CS1 is predictive of a US and that CS2 is not, the second phase begins. In this phase, the US is presented in association with CS2 and not with CS1.

In simulations of discrimination reversal with the dynamic model, the encoding of novel associations in the hippocampal network during the second phase increased encoding error, leading to some increase in medial septal activity and modifications of hippocampal stimulus representations. However, because both CS1 and CS2 were familiar and well encoded, the hippocampal learning rate was lower in the second phase than in the first phase, leading to slower acquisition (see Figure 8). These results are consistent with previous reports that acquisition in the second phase of discrimination reversal tasks is generally slower than acquisition in the first phase (e.g., see Berger & Orr, 1983; Miller & Steinmetz, 1997). In contrast, in previous simulations with a static corticohippocampal model, slightly fewer trials were required to learn the discrimination in the second phase (Gluck & Myers, 1993).

Figure 8c shows the predicted medial septal activity during the first and second phases of reversal learning. Medial septal activity increases at the onset of both phases. Because encoding error in the second phase is caused primarily by errors in predicting the US, the duration and magnitude of increased septal activity in the second phase is less than in the first phase. Similarly, neurophysiological measurements show much less hippocampal activity at the beginning of the second phase than at the beginning of the first phase (Miller & Steinmetz, 1997).

Blocking

A classical conditioning task that has been the focus of many empirical tests and theories in recent years is the Kamin (1969) blocking task. The blocking task traditionally consists of three phases. In the first phase, a CS (CS1) is paired with a US and the subject learns to respond to CS1. In the second phase, the subject is presented with a compound CS paired with the US. The compound CS consists of the previously trained CS1 and a novel CS (CS2). After the second phase, CS2 by itself is presented to the subject to test how many CRs are elicited to CS2 alone. There is typically less responding to CS2 in these "blocked" subjects than in subjects that were trained with the CS1–CS2 compound, but not with the CS1 alone. This suggests that CS1–US associations learned in the first phase interfere with the later formation (or recall) of CS2–US associations in the second (or third) phase.

Although the role of hippocampal processing in blocking is not well understood (Garrud et al., 1984; Kim, Krupa, & Thompson, 1998; Solomon, 1977), recent findings indicate that the septohippocampal system does play some role in this effect. In particular, blocking experiments conducted using animals with lesioned septohippocampal projections showed that the blocking effect is reduced by such damage (Baxter et al., 1999).

Both the static and dynamic corticohippocampal models show little generalization to CS2 in the third phase of simulated blocking

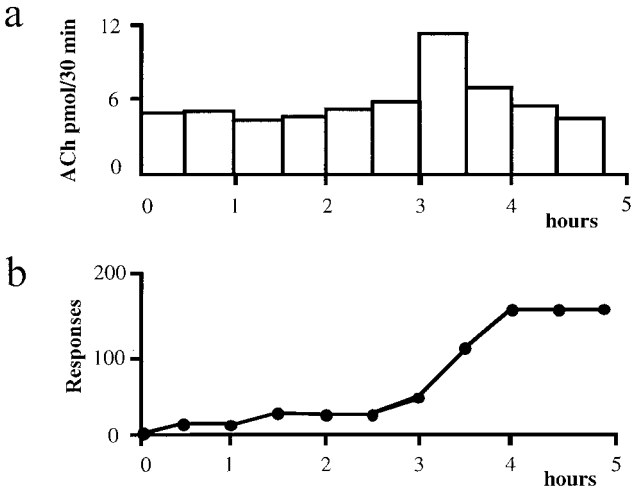

Figure 6. Increased hippocampal cholinergic levels precede increased leverpressing in a positively reinforced operant conditioning task. a: Levels of acetylcholine (ACh) during training. b: Number of responses during training. Reprinted from *Brain Research, 724*, M. Orsetti, F. Casamenti, and G. Pepeu, "Enhanced Acetylcholine Release in the Hippocampus and Cortex During Acquisition of an Operant Behavior," pp. 89–96, Copyright 1996, with permission from Excerpta Media, Inc.

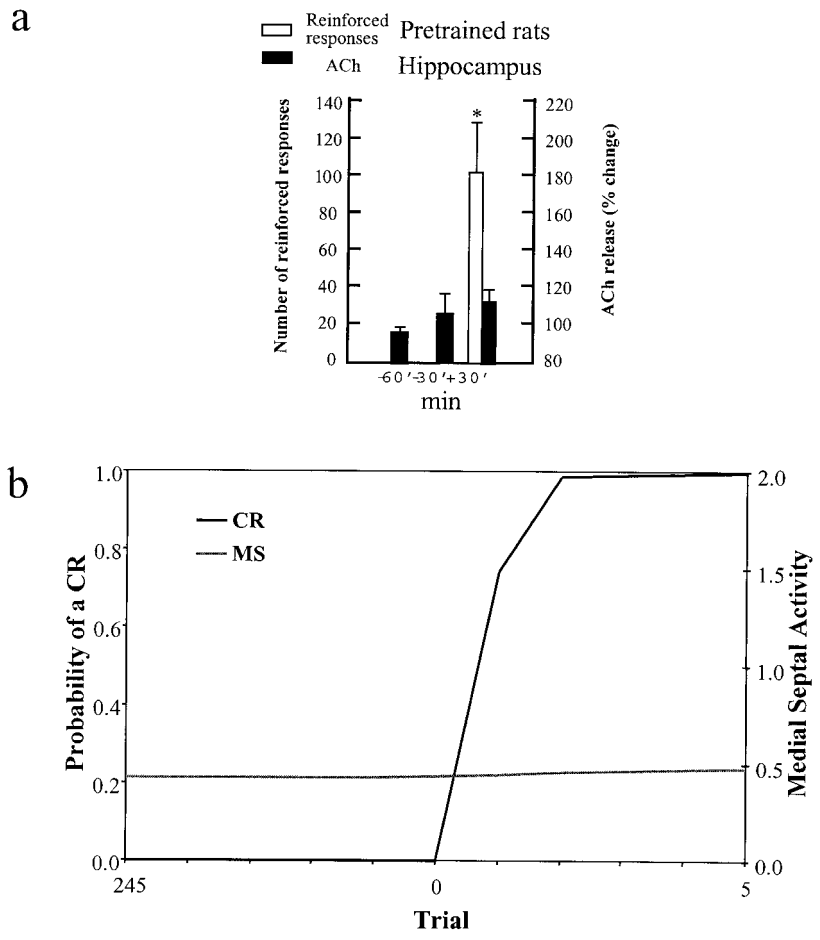

Figure 7. a: Mean (±*SEM*) number of reinforced responses and acetylcholine (ACh) levels during reacquisition of a conditioned response (CR). Cholinergic levels in the hippocampus do not increase during reacquisition. Reprinted from *Brain Research, 724,* M. Orsetti, F. Casamenti, and G. Pepeu, "Enhanced Acetylcholine Release in the Hippocampus and Cortex During Acquisition of an Operant Behavior," pp. 89–96, Copyright 1996, with permission from Excerpta Media, Inc. After training, rats were implanted with a microdialysis probe, and cholinergic levels were measured on reintroduction to the operant conditioning chamber. b: Reacquisition does not lead to changes in medial septal (MS) activity in the dynamic model. Asterisk indicates a significant difference in reinforced responses ($p < .01$).

tasks (see Figure 9). When two conditioned stimuli are presented together in the second phase, CS1 is already highly predictive of the US, and thus few changes are made in the hippocampal network relating CS2 to the occurrence of the US. Consequently, when CS2 is presented alone, it is a poor predictor of the US, and this observation is consistent with empirical findings.

Simulations of blocking in the dynamic corticohippocampal model show that changes in medial septal activity at the beginning of the second phase can potentially lead to decreases in conditioned responding (see Figure 9). After CS1 and CS2 have been presented together several times, the change in medial septal activity disappears, and conditioned responding returns to normal. Recent eyeblink conditioning experiments conducted in our laboratory have allowed us to examine whether such decreases occur at the beginning of the second phase of training. These experiments are described below.

Method. Ten male rabbits (*Oryctolagus cuniculus*; Covance Laboratories, PA) were used in this experiment. The rabbits were housed in individual cages in the Rutgers University Animal Facility (Newark, NJ). They were given free access to food and water and were maintained on a 12-hr light–dark cycle with light on at 7 a.m. All testing occurred between 8 a.m. and 6 p.m. Rabbits were divided into two training groups ($n = 5$ per group): (a) tone–light and (b) light followed by tone–light.

The rabbits were restrained in Plexiglas restraint boxes in individual conditioning chambers. Each chamber contained a speaker, air hose assembly, and eyeblink detection system. Presentations of the stimuli and recording of behavioral responses were controlled by a PC computer. The computer housed an interface board (Keithley Metrabyte, Taunton, MA) which triggered a set of relays that controlled the presentation of the tone CS and airpuff US based on software developed by Chen and Steinmetz (1998). Eyeblinks were monitored with an optoelectronic sensor that consisted of an LED and a phototransistor (for technical details see L. T. Thompson, Moyer, Akase, & Disterhoft, 1994). The LED emitted a beam of infrared light that was reflected off the cornea, and the reflectance of this beam was converted to a DC voltage by a phototransistor. The eyeblink signal was filtered (between 0.1 Hz and 1.0 kHz) and amplified (×100) by a differential AC amplifier (A-M Systems, Everett, WA). When the rabbit

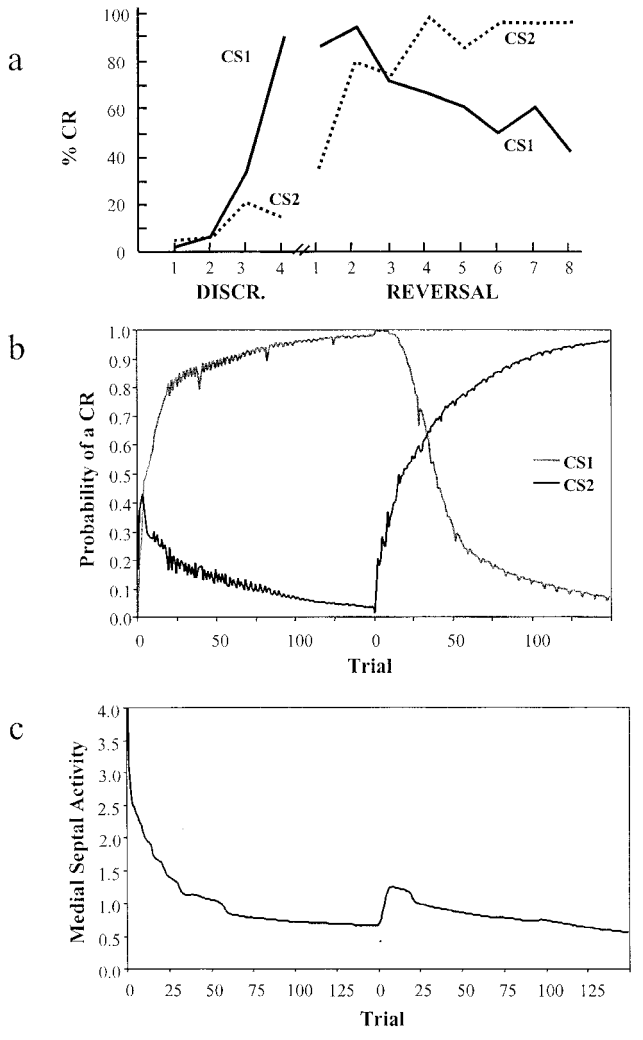

Figure 8. Acquisition in the second phase (Sessions 1–8) of a discrimination (DISCR.) reversal task is slower than in the first phase (Sessions 1–4) in (a) rabbit eyeblink conditioning (Reprinted from *Behavioural Brain Research, 8*, T. W. Berger and W. B. Orr, "Hippocampectomy Selectively Disrupts Discrimination Reversal Conditioning of the Rabbit Nictitating Membrane Response," pp. 49–68, Copyright 1983, with permission from Excerpta Media, Inc.) and (b) the dynamic corticohippocampal model. Note in Panel b that at the onset of the first phase there is generalization in that both Conditioned Stimulus 1 (CS1) and CS2 are equally likely to elicit a conditioned response (CR). Medial septal activity (in arbitrary units) increases in the dynamic model at the beginning of the second phase of training, but to a lesser degree than seen at the beginning of training (c).

closed its eye, the reflectance of the infrared beam changed and was recorded as an eyeblink. Any movement greater than 0.5 mm during the pre-CS period caused the training trial to be discarded from the analysis. A CR was scored if movement of greater than 0.5 mm was seen in the CS period.

The CS was either a 450-ms, 90-dB, 1000-Hz tone or a 450-ms, 12-V light delivered from a panel in front of the rabbit's face. The US was a 50-ms, 4 psi (27.6 kPa) corneal airpuff delivered via a rubber hose attached to the eyeblink detector assembly and aimed at the rabbit's cornea. All training trials were paired presentations in which the CS onset was 400 ms prior to the US onset, and the CS and US coterminated. The intertrial interval between training trials was a pseudorandom number around 25 s. All training was done in darkened chambers in a conditioning room illuminated by a red light.

Prior to acquisition, each rabbit was adapted to the conditioning chamber and restraint box for two daily sessions. On the 1st day of adaptation, the rabbit was placed in the restraint box in the conditioning chamber for 30 min. On the 2nd day of adaptation, the rabbit was placed in the restraint box in the conditioning chamber for 45 min with the eyeblink detector aimed at the cornea.

Acquisition consisted of two phases of training. Phase 1 consisted of 700 trials over seven consecutive daily sessions. The tone blocking group received tone–airpuff training with an interstimulus interval (ISI) of 400 ms between the onset of the light and the onset of the airpuff. The light blocking group received light–airpuff training with an ISI of 400 ms between the onset of the light and the onset of the airpuff. The light control group and tone control group received 700 "trials" in which no stimuli were presented. Phase 2 consisted of 500 trials over five consecutive daily sessions. All four groups received tone–light–airpuff training in which the tone and light were presented simultaneously, with an ISI of 400 ms between the onset of the tone–light and the onset of the airpuff.

Results. In Phase 1 training, there was a significant difference in conditioned responding across sessions, $F(13, 104) = 43.60$, $p < .01$, such that rabbits exhibited more CRs as training progressed. There was also a significant difference in conditioned responding between the conditioned stimuli, $F(1, 8) = 7.47$, $p < .01$, such that there was more conditioned responding overall to the

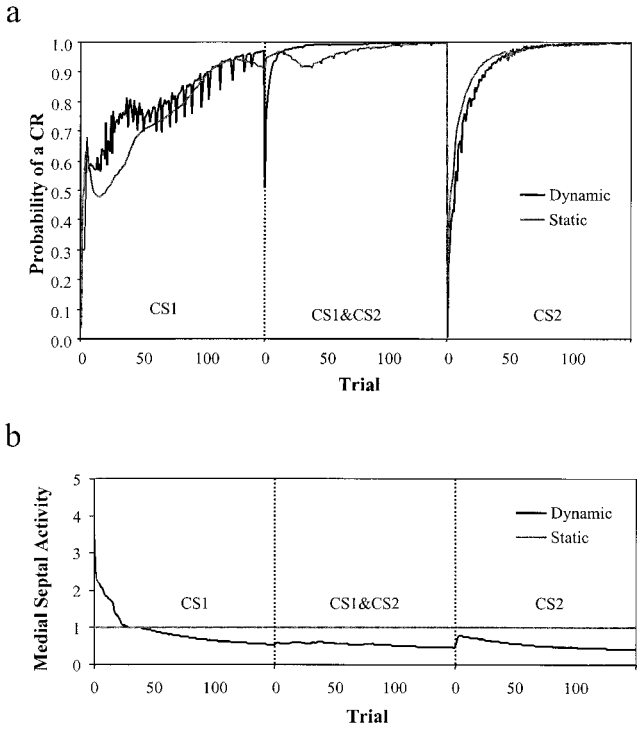

Figure 9. a: The dynamic model shows a decrease in conditioned responding to the novel stimulus in the initial trials of the second phase of conditioning, whereas the static model does not. Both models show little generalization to Conditioned Stimulus 2 (CS2) in the third phase. b: Medial septal activity (in arbitrary units) increases slightly at the beginning of the second phase of training in the dynamic model and to a greater degree at the beginning of the third phase. CR = conditioned response.

tone than to the light. Finally, there was a significant interaction of Stimuli × Session, $F(13, 104) = 4.49$, $p < .01$, indicating that CRs to the tone and light were learned at different rates (see Figure 10a). In Phase 2, there was not a significant difference in conditioned responding across sessions, $F(9, 72) = .77$, $p > .50$, nor in conditioned responding between stimuli, $F(1, 8) = 2.95$, $p > .10$, and there was no Stimuli × Session interaction, $F(9, 72) = 0.80$, $p > .60$.

To test for a decrement between Phase 1 and Phase 2, the last 10 trials of Phase 1 were compared with the first 10 trials of Phase 2 by using a *t* test. For the light followed by tone–light training group, there was a significant difference in conditioned responding between the end of Phase 1 and the start of Phase 2, $t(4) = 10.95$, $p < .01$, such that there was less responding at the start of Phase 2 than at the end of Phase 1. For the tone followed by tone–light training, there was no significant difference in conditioned responding between the end of Phase 1 and the start of Phase 2, $t(4) = -0.62$, $p > .50$. Overall, for the end of Phase 1, there was no significant difference in conditioned responding between the light and tone conditions. However, for the start of Phase 2, there was a significant difference in conditioned responding between light and tone conditions, $t(4) = 6.90$, $p < .01$, such that there was less responding to the tone–light compound in the group previously trained to the light than there was in the group previously trained to the tone (see Figure 10b).

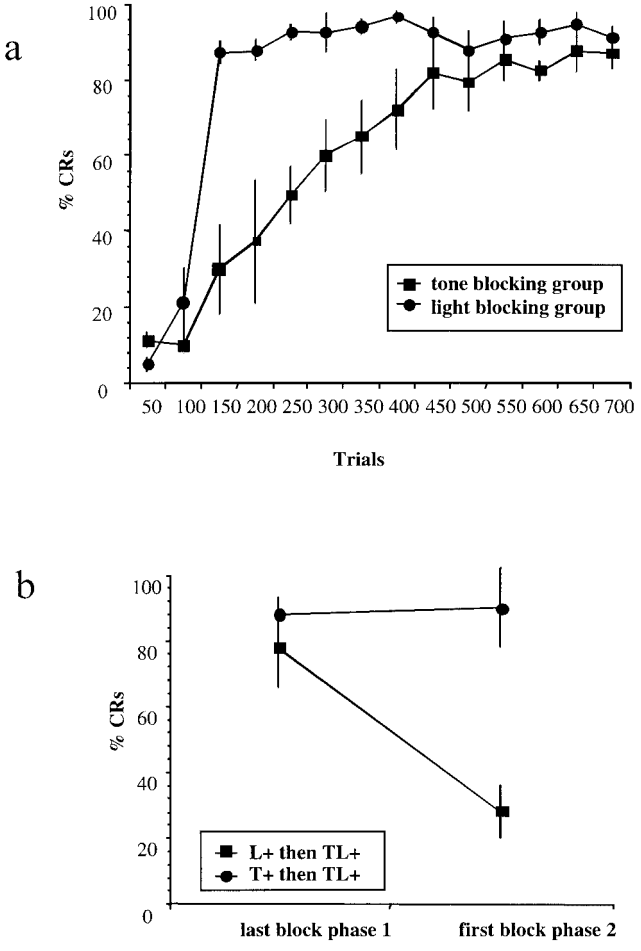

Figure 10. Conditioned responding in rabbits during the first two phases of a blocking task involving classically conditioned eyeblinks. The tone blocking group was first trained to respond to a light (L+), and then to a tone and light presented simultaneously (TL+). The light blocking group was first trained to respond to a tone (T+), and then to a tone and light. a: Rabbits learned to respond to tones more quickly than to lights in Phase 1, suggesting that the tones were more salient. b: Conditioned responding decreased at the beginning of Phase 2 in rabbits initially trained to respond to a light, but not in rabbits initially trained to respond to a tone. Error bars represent *SE*. CR = conditioned response.

Discussion. When rabbits were switched from being trained to respond to a light to being trained to respond to a tone–light compound, there was a significant decrease in conditioned responding, consistent with the predictions of the dynamic corticohippocampal model. This decrease was not observed, however, in rabbits that were initially trained to respond to a tone. Because there was faster acquisition of conditioned responses to the tone than to the light, it appears that the tone is a more salient stimulus than the light (at least for the parameters used in this study). This suggests that if the salience of the added cue is weaker than the initially trained cue, a decrement in conditioned responding will not occur at the beginning of Phase 2. The results of our simulations suggest that a decrement in conditioned responding at the start of Phase 2 will not occur if medial septal activity is fixed during the transition from Phase 1 to Phase 2 in the blocking task (see Figure 9). Our model thus predicts that changes in medial septal activity evoked by switching from light–US training to light–tone–US training will be greater than changes in activity evoked by switching from tone–US training to light–tone–US training. The model further predicts that a novelty-induced reduction in CRs at the start of Phase 2 can be blocked by preventing changes in medial septal activity (e.g., by lesioning hippocamposeptal connections or blocking neurotransmission). Additional studies examining how the salience of a stimulus affects septohippocampal responses to novelty are clearly needed.

General Discussion

In this article, hippocamposeptal feedback has been incorporated into the Myers et al. (1996) model of septohippocampal modulation during associative learning, resulting in a more complete characterization of septohippocampal dynamics during conditioning. Hippocamposeptal feedback is instantiated in the corticohippocampal model by dynamically adjusting the learning rate in the hippocampal network (but not in the cerebellar cortical network) on the basis of how well stimulus representations are encoded in this network. Both novel stimuli and novel associations between stimuli generate larger encoding errors, which lead to higher learning rates, which ultimately facilitate faster encoding of stimulus representations. This self-regulating process is based on the mechanisms of septohippocampal interaction postulated by Hasselmo and colleagues (Hasselmo & Schnell, 1994; Hasselmo, 1995). The resulting model correctly accounts for behavioral and physiological data from studies of both classical and operant conditioning. Specifically, the model accounts for observations that (a) disruption of hippocamposeptal feedback does not prevent acquisition of conditioned responses, but does retard learning; (b) increases in evoked medial septal activity precede conditioned changes in behavioral responses and levels of medial septal activ-

ity decrease over the course of training (i.e., as stimuli become more familiar); (c) medial septal activity does not increase during reacquisition of an extinguished operant response; (d) duration and magnitude of medial septal activity increase at the beginning of the second phase of discrimination reversal learning, but to a considerably lesser degree than in the first phase; and (e) introduction of a novel, salient stimulus, in combination with a familiar stimulus, leads to a decrease in conditioned responding in the second phase of blocking. The model further predicts that cholinergic levels gradually decrease in the hippocampus as acquisition of a conditioned response progresses, that medial septal activity is low during extinction, and that the disruption of CRs evoked at the beginning of the second phase of the blocking task can be blocked by disrupting hippocamposeptal feedback or by familiarizing subjects with CS2 prior to training.

Relation to Other Computational Models of Septohippocampal Function

Past computational models of septohippocampal processing have often been designed to characterize detailed biophysical–circuit level dynamics affecting memory formation (Hasselmo, 1995; Menschik & Finkel, 1998). For example, much attention has been given to modeling how variation in levels of acetylcholine and GABA influence theta rhythm oscillations in the hippocampus (Denham & Borisyuk, 2000; Hasselmo et al., 1996; Wallenstein & Hasselmo, 1997). Such oscillations are thought to play a critical role in septohippocampal processing (for review, see Hasselmo, 2000). One limitation of this approach is that the dynamics of septal neuromodulation in behaving animals are currently not well characterized. For example, effects once thought to depend on cholinergic modulation are now attributed to GABAergic modulation (Alreja, Wu, Atkins, Leranth, & Shanabrough, 2000; Wu, Shanabrough, Leranth, & Alreja, 2000), and the roles of dopamine, serotonin, norepinephrine, and various neuropeptides are currently not accounted for in these biologically based models (Walsh, 2000). How chemical or physical alterations affect these dynamics is also poorly understood. Complex interactions between neuromodulators can lead to comparatively simple outcomes, such as increases or decreases in the adaptability or excitability of hippocampal neurons. In the present model, we have attempted to characterize such functional outcomes of septohippocampal modulation, without incorporating details of the electrochemical mechanisms underlying these outcomes. Both biophysical and process-level approaches can provide useful information toward understanding the role of septohippocampal processing in learning and memory. The biological plausibility of our model rests on the accuracy of biologically based simulations conducted by Hasselmo and colleagues (Hasselmo & Schnell, 1994; Hasselmo & Wyble, 1997), from which our implementation of hippocamposeptal feedback was derived. Whether such biologically realistic models can accurately predict the effects of conditioning on behavior and neurophysiology is an important issue for future research to address.

Several biologically inspired, novelty-driven learning algorithms have been developed in the past (Borisyuk et al., 2001; den Dulk, Rokers, & Phaf, 1996; Japkowicz et al., 1995; Sutton & Barto, 1981), and an extensive literature exists in the area of dynamic learning rates (Cater, 1987; Carter et al., 1998; Luo, 1987; Silva & Almeida, 1990). Dynamic learning algorithms are typically used to increase the speed and effectiveness of training relative to training with static algorithms. Although impressive gains in acquisition speed can sometimes be achieved, dynamic learning algorithms are often unstable. In the present model, however, there appeared to be a self-regulating effect, leading to stability. Including hippocamposeptal feedback in the corticohippocampal model enhanced acquisition, despite the fact that the learning rate was, on average, lower than in the static model (see Figure 5). Throughout training, the dynamic model generated a higher percentage of correct responses and, consequently, reached criterion sooner than the static model. Other dynamic learning algorithms may have worked as well as the one we chose. For example, some success has been attained with systems in which learning rate decreases simply as a function of time (Hinton & Sejnowski, 1986; Kohonen, 1997; Sohal & Hasselmo, 1998). Identifying which algorithm most closely parallels neural processing was not a goal of our study. Rather, we focused on assessing whether adding a feedback loop to an existing model of septohippocampal processing would increase its ability to predict and explain behavioral and physiological phenomena.

Earlier neural network models of septohippocampal processing in conditioning have proposed somewhat different mechanisms from the ones implemented in our model. In particular, Schmajuk and colleagues have developed a computational model that accounts for many of the same findings from classical conditioning experiments that our model does (Buhusi & Schmajuk, 1996; Schmajuk et al., 1994; Schmajuk, 1997). Similarities and differences between the Schmajuk (Schmajuk & DiCarlo, 1992) model and the Gluck and Myers (1993) model have been previously discussed in detail (Myers et al., 1995). A main difference between these models is how they characterize septohippocampal interactions. The Schmajuk model assumes that the medial septum provides an error signal to the hippocampus that is used to regulate learning in cortical networks, whereas our dynamic model assumes that the hippocampus provides an error signal to the medial septum to self-regulate hippocampal encoding of stimulus representations. Additionally, our model assumes that novelty detection plays a critical role in septohippocampal interactions, whereas the Schmajuk model assumes that novelty is computed in the nucleus accumbens and plays no role in septohippocampal interactions. These differences lead to disparate predictions regarding how septohippocampal disruption should affect conditioning. In particular, in the Schmajuk model, formation of new stimulus representations cannot occur if projections from the medial septum are eliminated, whereas our model predicts that such damage would simply retard learning. The Schmajuk model also predicts that stimulus novelty should have little effect on medial septal (or hippocampal) activity, contrary to the predictions of our model.

Relation to Theories of Attention in Conditioning

Past theoretical accounts of the role novelty plays in conditioning have focused on how it affects attentional processes (e.g., see Pearce & Hall, 1980). For example, familiarity with a stimulus is thought to retard acquisition of a conditioned eyeblink response because the subject has previously learned to ignore nonpredictive stimuli. Slow extinction rates have also been postulated to result from attentional effects (e.g., Krushcke & Johansen, 1999).

Additionally, performance in multiphase conditioning tasks has been explained in terms of interactions between stimulus novelty and stimulus relevance (or predictive novelty) (Rescorla & Wagner, 1972; Pearce & Hall, 1980). The Rescorla–Wagner learning rule (Rescorla & Wagner, 1972) suggests that the effectiveness of conditioning depends primarily on the novelty of the conditioned stimulus, whereas Pearce and Hall (1980) suggest that conditioning depends primarily on the ability of the CS to predict the US. Our dynamic corticohippocampal model incorporates aspects of both of these learning theories. During acquisition, both novelty of the CS and novelty of the CS–US relationship determine the learning rate, and thus the rate of CR acquisition. The previous model of septohippocampal processing developed by Myers et al. (1996) does not incorporate such a general mechanism. In the static model, each node is only modified to the extent that it is a source of encoding error (as a consequence of back-propagation); no general error measure influences this process. Simulations with the dynamic model suggest that learned inattention may manifest itself neurobiologically in the form of reduced medial septal activation during early phases of conditioning with familiar stimuli.

Implications for Other Neural Processes

The self-regulatory processes implemented in our model probably play a role in other neural systems involved in learning and memory. For example, connections between the medial septum and the entorhinal cortex are similar to septohippocampal connections (Hasselmo & Wyble, 1997; Hasselmo, Fransen, Dickson, & Alonso, 2000). Connections between several neocortical areas and neuromodulatory centers in the basal forebrain have been found to be either directly or indirectly reciprocal (Zaborszky, Gaykema, Swanson, & Cullinan, 1997; Zaborszky, Pang, Somogyi, Nadasdy, & Kallo, 1999). Models of experience-induced plasticity in sensory cortical networks suggest that reorganization is modulated by neurons in a part of the basal forebrain known as the nucleus basalis (Weinberger et al., 1990; Mercado, Myers, & Gluck, 2001) and that activation of these neurons is regulated by the cortical networks they innervate (for review, see Weinberger, 1998).

Comparative analyses of the different roles medial septal neurons and nucleus basalis neurons play in conditioning can clarify whether similar self-regulatory mechanisms are used throughout the basal forebrain. A critical question is how modulation of plasticity in cortical networks and modulation of information processing in the hippocampal system are coordinated at the level of the basal forebrain. Experiments investigating correlations between activity in medial septum and nucleus basalis neurons during conditioning may shed light on how these systems interact, as may experiments examining the effects of hippocampal lesions on experience-induced cortical plasticity. Computational models of corticohippocampal dynamics that are constrained by both behavioral and neuroscientific data can provide a deeper understanding of how basal forebrain neurons influence representations and recollections of stimulus events.

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