

# Dissociating Basal Forebrain and Medial Temporal Amnesic Syndromes: Insights from Classical Conditioning

CATHERINE E. MYERS<sup>1</sup>  
DEBORAH BRYANT<sup>2</sup>  
JOHN DELUCA<sup>3</sup>  
MARK A. GLUCK<sup>4</sup>

<sup>1</sup>*Department of Psychology, Rutgers University, Newark, NJ*

<sup>2</sup>*Kessler Medical Rehabilitation Research and Education Corporation, West Orange, NJ*

<sup>3</sup>*Kessler Medical Rehabilitation Research and Education Corporation, West Orange, NJ  
Department of Physical Medicine and Rehabilitation, University of Medicine and Dentistry  
of New Jersey–New Jersey Medical School, Newark, NJ*

<sup>4</sup>*Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, NJ*

In humans, anterograde amnesia can result from damage to the medial temporal (MT) lobes (including hippocampus), as well as to other brain areas such as basal forebrain. Results from animal classical conditioning studies suggest that there may be qualitative differences in the memory impairment following MT vs. basal forebrain damage. Specifically, delay eyeblink conditioning is spared after MT damage in animals and humans, but impaired in animals with basal forebrain damage. Recently, we have likewise shown delay eyeblink conditioning impairment in humans with amnesia following anterior communicating artery (ACoA) aneurysm rupture, which damages the basal forebrain. Another associative learning task, a computer-based concurrent visual discrimination, also appears to be spared in MT amnesia while ACoA amnesics are slower to learn the discriminations. Conversely, animal and computational models suggest that, even though MT amnesics may learn quickly, they may learn qualitatively differently from controls, and these differences may result in impaired transfer when familiar information is presented in novel combinations. Our initial data suggests such a two-phase learning and transfer task may provide a double dissociation between MT amnesics (spared initial learning but impaired transfer) and ACoA amnesics (slow initial learning but spared transfer). Together, these emerging data suggest that there are subtle but dissociable differences in the amnesic syndrome following damage to the MT lobes vs. basal forebrain, and that these differences may be most visible in non-declarative tasks such as eyeblink classical conditioning and simple associative learning.

## Introduction

ANTEROGRADE AMNESIA IS A neuropsychological syndrome defined by a dense memory impairment with relative sparing of other cognitive function such as intelligence, attention,

---

Address for Correspondence: Dr. Catherine E. Myers, Memory Disorders Project at Rutgers University–Newark, 197 University Avenue, Newark, NJ 07102.

*Integrative Physiological & Behavioral Science*, April–June 2002, Vol. 37, No. 2, 85–102.

and judgment. The classic anterograde amnesia syndrome has three basic components. First, amnesic patients are severely impaired in the ability to form new declarative memories—memories for facts or events. Second, amnesic patients show spared ability to form new non-declarative memories—memories that encode procedures or habits. Third, although amnesic patients may show some time-graded retrograde amnesia, declarative memories formed before the amnesia-inducing events are often left intact and accessible.

In humans, anterograde amnesia has been observed following damage to at least three distinct brain regions: the medial temporal lobes, including hippocampus and associated structures; the basal forebrain, including the medial septum/diagonal band complex; and structures associated with the diencephalon. Medial temporal amnesia is by far the best-studied form of anterograde amnesia, with a wealth of data from both human subjects and animal models (for a review, see Squire, 1991). Diencephalic amnesia is less well-understood, with most cases occurring in individuals with Wernicke/Korsakoff syndrome (see Kopelman, 1995) associated with chronic alcohol abuse. Thus, it is difficult to determine which cognitive deficits are specifically due to the diencephalic damage as opposed to the wealth of other kinds of brain damage arising from alcohol abuse and associated malnutrition.

The third form of amnesia, basal forebrain amnesia, was only identified in humans as recently as the 1980s (Gade, 1982; Alexander & Freedman, 1984; Damasio et al., 1985). The basal forebrain consists of several structures, including the medial septum/diagonal band complex and nucleus basalis of Meynert. The few cases in which lesions can be localized to specific basal forebrain structures suggest that damage limited to the medial septum and/or diagonal band, but sparing the nucleus basalis, is sufficient to cause amnesia (e.g., Phillips, Sangalang & Sterns, 1987; Morris et al., 1992; Abe et al., 1998). Given the rarity of such naturally-occurring cases, it has been difficult to delineate the precise role of these basal forebrain structures in human amnesia.

However, there is a sizeable body of animal literature reporting memory deficits following basal forebrain damage, particularly to the medial septum/diagonal band complex (see Everitt & Robbins, 1997). The existence of this animal literature provides a starting point for understanding potential differences between basal forebrain amnesia and medial temporal amnesia. This emerging dissociation between basal forebrain amnesia and medial temporal amnesia is the focus of this article.

The simplest, “textbook” view of anterograde amnesia is that all three brain regions—the medial temporal lobes, basal forebrain, and diencephalon—are critical components of a single memory system, and that damage to any one of these areas can result in a unified syndrome of anterograde amnesia. In other words, it may not matter where the actual damage is, the amnesia will be the same. In fact, patients who become amnesic following damage to any of these brain regions do show superficial similarity: specifically, devastated declarative memory with relative sparing of non-declarative memory and other cognitive function.

However, data from animal models suggest a more complicated story. There are qualitative differences in the learning behaviors of animals with hippocampal-region damage vs. basal forebrain damage, and these qualitative differences are evident even in the most basic forms of non-declarative learning, such as classical conditioning. The fact that such differences exist suggests that while various brain regions may all participate (and even cooperate) in normal learning, each brain region may contribute distinct components to that learning.

### **Classical Eyeblink Conditioning: A Model System**

Classical eyeblink conditioning involves a corneal airpuff or paraorbital shock (the unconditioned stimulus or US) which reliably evokes a reflexive eyeblink. If the US is repeatedly preceded by a neutral stimulus, such as a tone or light (the conditioned stimulus or CS), the CS itself can come to evoke a protective eyeblink (the conditioned response or CR) at the time of anticipated US arrival. In the widely-studied delay conditioning paradigm, the CS and US overlap and co-terminate. Eyeblink classical conditioning is one of the most well-characterized forms of learning, with parametric effects and neurobiological substrates that are largely consistent across a range of species including humans (Gormezano et al., 1984; Thompson, 1986).

Specifically, the cerebellum appears to be the necessary substrate for learning of a well-timed delay eyeblink CR (Solomon, Lewis et al., 1986; Thompson, 1986). Thompson (1986) proposed that CS information from the pontine nuclei travels via mossy fibers to the cerebellar Purkinje cells and interpositus nuclei, which in turn produce output that drives the behavioral CR. Plasticity is assumed to occur at the sites where CS information converges on the Purkinje cells and the interpositus nuclei. Thompson (1986) further proposed that this learning is driven by an error signal, computed by the inferior olive, which reflects the difference between the US and CR. This signal then travels to the Purkinje cells and interpositus nuclei and modifies synapse strength according to conjoint presynaptic and postsynaptic activity and in proportion to the error signal. This learning rule can be formalized as the least mean square (LMS) algorithm (Widrow & Hoff, 1960), which has similarity both to biological mechanisms of plasticity such as long-term potentiation and depression (Levy, Brassel & Moore, 1983; Donegan, Gluck & Thompson, 1989) and to mathematical specifications of conditioning (Rescorla & Wagner, 1972; Sutton & Barto, 1981; Gluck & Bower, 1988).

The Thompson (1986) model of the cerebellar substrates of eyeblink conditioning has been formalized as a connectionist network, as shown in Figure 1A (Gluck, Myers & Thompson, 1994; Allen, Myers & Gluck, 2001). The network learns to map from inputs representing sensory information to a pattern of activations on a series of nodes representing the Purkinje cell layer; these nodes project to an output layer, representing the interpositus nuclei, which in turn produces output to drive the CR. The weights from the internal (Purkinje) to output (interpositus) layer are modified proportional to the error signal (US-CR) computed by the inferior olive. This computational model is sufficient to account for development of a well-timed CR in the delay conditioning paradigm, as well as for various other conditioning-related phenomena such as conditioned inhibition and blocking (Allen, Myers & Gluck, 2001).

Given that the cerebellum is a sufficient substrate for delay eyeblink conditioning, it is not surprising that delay eyeblink conditioning is spared following hippocampal damage in both animals (Schmaltz & Theios, 1972; Solomon & Moore, 1975; Akase, Alkon & Disterhoft, 1989) and humans (Weiskrantz & Warrington, 1979; Woodruff-Pak, 1993; Gabrieli et al., 1995); that is, lesioned subjects acquire the CR at the same rate as control subjects. The simplest interpretation of these results is that the hippocampus and associated medial temporal lobe structures are simply “not needed for” or “not involved in” delay eyeblink conditioning.

However, recording studies by Berger et al. (1983) showed that, even during this simple form of associative learning, the hippocampus is indeed active. In an animal that has learned the CS-US association and is reliably giving a CR, there is activity in the hippoc-

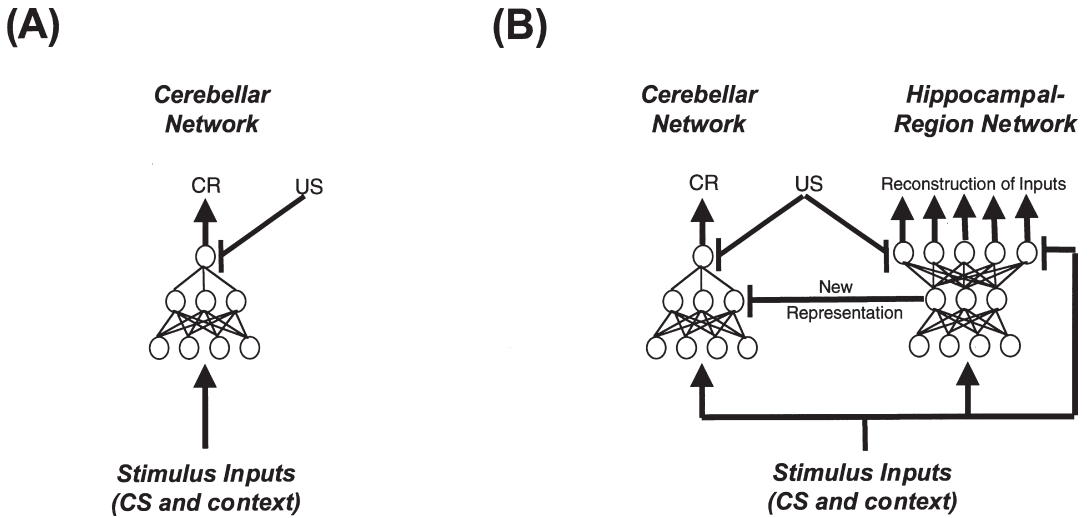


FIG. 1. (A) A computational model of the cerebellar substrates of conditioning (based on Gluck, Myers & Thompson, 1994). (B) Extension of this model to include a role for the hippocampal-region (based on Gluck & Myers, 1993).

ampus that mirrors and precedes the behavioral response. This activity is not visible in an untrained animal given the CS or US alone, confirming that the hippocampal response really does reflect the learned CS-US association. Later studies using functional neuroimaging have likewise confirmed similar learning-associated activity in the human hippocampus during eyeblink conditioning (Logan & Grafton, 1995; Blaxton et al., 1996).

These results suggest that, although the hippocampus may not be strictly needed for delay eyeblink conditioning, it nevertheless does normally contribute to such learning. The next question to address is what the nature of this contribution might be.

### A Computational Model of Cortico-Hippocampal Function

One possible account of the role of hippocampal-region structures in conditioning was provided by Gluck and Myers (1993, 2001) in a computational model, as shown in Figure 1B. In addition to the cerebellar network, this model contains a second network representing some aspects of hippocampal-region function. Like the cerebellar network, the hippocampal-region module has an input layer which receives sensory information and projects to an internal node layer; these nodes in turn project to an output node layer. The output nodes generate a prediction of the US as well as reconstructing the sensory inputs. Because the internal node layer is narrower than the input or output layers, the network is forced to construct representations in the internal node layer that compress redundant information, such as cues that reliably co-occur or make similar predictions about future US arrival, while preserving and differentiating non-redundant information. For example, if two cues A and B always co-occur and predict the US, then the network will tend to compress their representations into a single compound stimulus AB. On the other hand, if two superficially similar stimuli A and A' make opposing predictions about the US—A predicts the US but A' does not—the network will tend to differentiate their representations, making it easier to map A and A' to different behavioral responses.

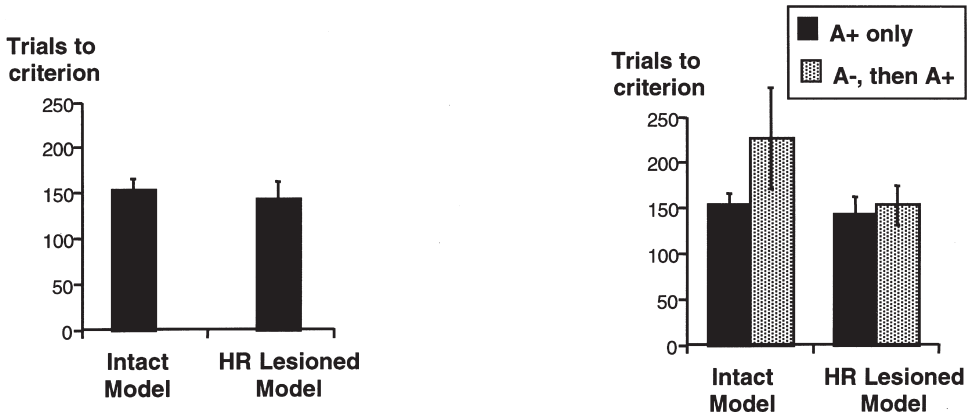
**(A) Simple Acquisition****(B) Latent Inhibition**

FIG. 2. Simulation results from the cerebellar-hippocampal model of Figure 1B (Gluck & Myers, 1993). (A) Simple acquisition of a CS-US association is not impaired by hippocampal-region (HR) lesion in the model. (B) The intact but not HR-lesion model shows latent inhibition.

In the computational model, the cerebellar and hippocampal-region networks interact. The hippocampal-region network forms new stimulus representations biased to compress redundant information while differentiating predictive information. These new representations are provided to the cerebellar network, which then learns to generate appropriate behavioral responses based on these representations. Over time, the cerebellar network adopts the hippocampal-generated representations, so that inputs to the cerebellar network evoke the appropriate representations directly in the cerebellar network's hidden nodes.

Hippocampal-region lesion can be simulated in this computational model by simply disabling the hippocampal-region network (in effect, reverting to the cerebellar model of Figure 1A). In this case, the cerebellar network can no longer adopt any new hippocampal-mediated representations. It can, however, still make use of those representations that it has already adopted. New learning will be impaired or spared according to whether the pre-existing cerebellar representations are sufficient. In the case of simple delay conditioning, learning to map from a single stimulus A to a CR, any *a priori* cerebellar representations are likely to suffice; thus, the computational model correctly captures the fact that simple delay eyeblink conditioning is spared after hippocampal-region damage (Figure 2A). However, more complex eyeblink conditioning paradigms, which require hippocampal-mediated representations may be disrupted.

One example is latent inhibition. In latent inhibition, prior exposure to an unreinforced stimulus (A-) retards subsequent learning that that stimulus predicts the US (A+). Latent inhibition has been observed in delay eyeblink conditioning in rabbits (Shohamy et al., 2000), rats (Schmajuk, Lam & Christiansen, 1994) and humans (Allen et al., 2002). Latent inhibition is abolished following hippocampal-region damage in rabbits (Shohamy et al., 2000) and rats (Schmajuk et al., 1994). In humans, medial temporal amnesia disrupts a computer-based task that embeds the logical structure of latent inhibition (Myers, McGlinchey-Berroth et al., 2000).

In the model, during A—exposure, the hippocampal-region network compresses the representation of A together with the representation of other co-occurring contextual cues—since all are equally predictive that no US will occur. Later, when A predicts the US, this representational compression must be explicitly undone to allow mapping A to one behavioral response (CR) and the contextual cues to the opposite response (no CR). This slows A+ learning relative to a condition with no exposure (Myers & Gluck, 1994). Since this explanation of latent inhibition depends on hippocampal-mediated representations, latent inhibition is correctly abolished in the hippocampal-lesioned model (Figure 2B).

The computational model of Figure 1 accounts for a range of eyeblink conditioning data from intact and hippocampal-lesioned animals (Gluck & Myers, 1993, 2001; Myers & Gluck, 1994); it has also been extended to other domains such as human category learning (Gluck, Oliver & Myers, 1996) and rodent odor discrimination (Myers & Gluck, 1996).

### **Contributions of Basal Forebrain**

In later work, this computational model was extended to include a third important brain region: the basal forebrain. Within the basal forebrain, the medial septum/diagonal band complex projects to the hippocampus, providing cholinergic and GABAergic inputs that affect hippocampal activity and plasticity. Disrupting septal activity, as by administration of the anticholinergic drug scopolamine into medial septum, affects hippocampal neuronal activity (Stumpf, Petsche & Gogolak, 1962). Arguing from such neurophysiological and behavioral evidence, Hasselmo and colleagues suggested that one role of the septohippocampal cholinergic projections is to modulate hippocampal processing (e.g., Hasselmo & Bower, 1993; Hasselmo & Schnell, 1994; Hasselmo, 1995). Specifically, they suggested that high levels of septohippocampal acetylcholine may increase the rate at which new information is processed and stored by the hippocampus.

This idea can be incorporated into the cortico-hippocampal model as shown in Figure 3A (Myers, Ermita et al., 1996, 1998), by adding a medial septal module that projects to the hippocampal-region network and governs the rate at which the hippocampal-region network learns new information. In this case, lesioning the medial septum has the effect of disrupting hippocampal-region processing—even though the hippocampus itself is not directly damaged. As a result, the hippocampal-region outputs to long-term storage areas such as cerebellum are also disrupted, impairing the ability to learn even simple CS-US associations. Thus, in the computational model, disrupting the hippocampus via septal lesion impairs acquisition of the CR—even though direct hippocampal damage does not. This result, shown in Figure 3B, is consistent with findings in animals and humans that medial septal lesion or disruption via scopolamine disrupts classical delay eyeblink conditioning, even though direct hippocampal lesion spares the effect (Berry & Thompson, 1979; Solomon et al., 1983, 1993).

The animal data from classical delay eyeblink conditioning suggest that this simple paradigm can be used to dissociate the effects of hippocampal lesion vs. medial septal lesion. Specifically, septal lesion retards CR acquisition while hippocampal lesion does not. The computational model suggests why this distinction might hold. The next question is whether such a simple distinction might be visible in human medial temporal vs. basal forebrain amnesia.

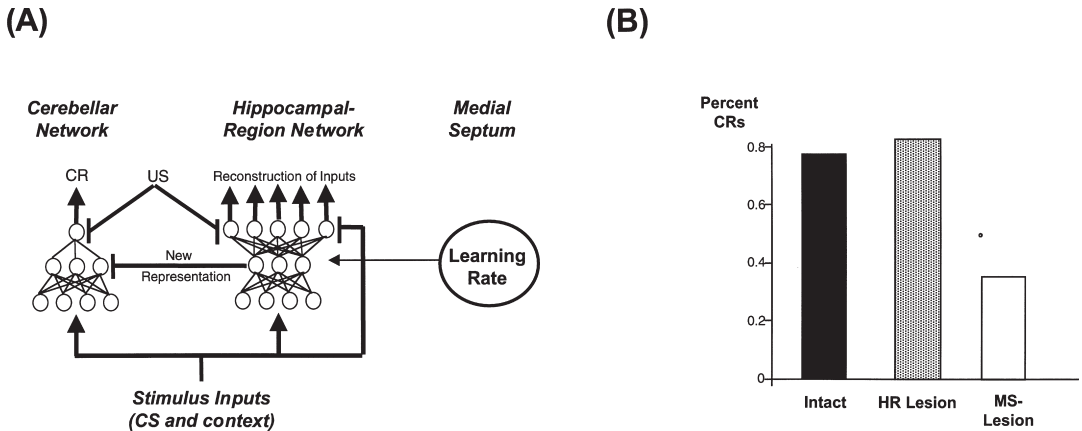


FIG. 3. (A) Extension of the cerebellar-hippocampal model to include a role for medial septum as modulating learning rates in the hippocampal-region network (Myers, Ermita et al., 1996, 1998). (B) This model correctly accounts for the finding that medial septum (MS) lesion or disruption retards simple CS-US learning even though outright hippocampal-region (HR) damage does not.

### Eyeblink Conditioning and Amnesia

There is already a considerable body of research documenting spared delay eyeblink conditioning in medial temporal amnesia. Specifically, individuals with medial temporal amnesia acquire the eyeblink CR at the same rate, and to the same asymptotic levels, as matched control subjects (Weiskrantz & Warrington, 1979; Woodruff-Pak, 1993; Gabrieli et al., 1995; Clark & Squire, 1998). Other paradigms, such as trace eyeblink conditioning, in which the CS terminates before US onset, can indeed be disrupted in medial temporal amnesia (e.g., McGlinchey-Berroth, Carrillo et al., 1997; Clark & Squire, 1998). However, it seems that in humans as in animals, the hippocampus and related structures are not strictly needed for acquiring a simple CS-US association in the delay conditioning paradigm.

The existing animal and computational data, summarized earlier, predict the opposite for individuals with basal forebrain amnesia: damage to the basal forebrain, specifically the medial septum/diagonal band complex, should disrupt hippocampal processing and thereby retard—though not abolish—delay eyeblink conditioning.

To test this prediction, we recently conducted a study of delay eyeblink conditioning on a group of six individuals who became densely amnesic following an ACoA aneurysm as well as a group of six healthy controls, matched for age and gender (Myers, DeLuca et al., 2001). Subjects were given 70 trials, pairing a 500 ms, 1000 Hz 72 dB tone CS with a 100 ms, 6.9 kPa airpuff US; the CS and US co-terminated. Any eyeblinks occurring from 100 msec after CS onset but before US onset were scored as CRs. After 10 such CS-US pairings, most control subjects were reliably giving CRs; across all 70 training trials, the control group averaged a total of over 70 percent CRs. In contrast, the ACoA amnesic group averaged only about 30 percent CRs—although they did show some slow improvement across the experiment (Figure 4). Perhaps given extended training they, like animals with medial septal lesion, would approach the same asymptotic performance levels as controls.

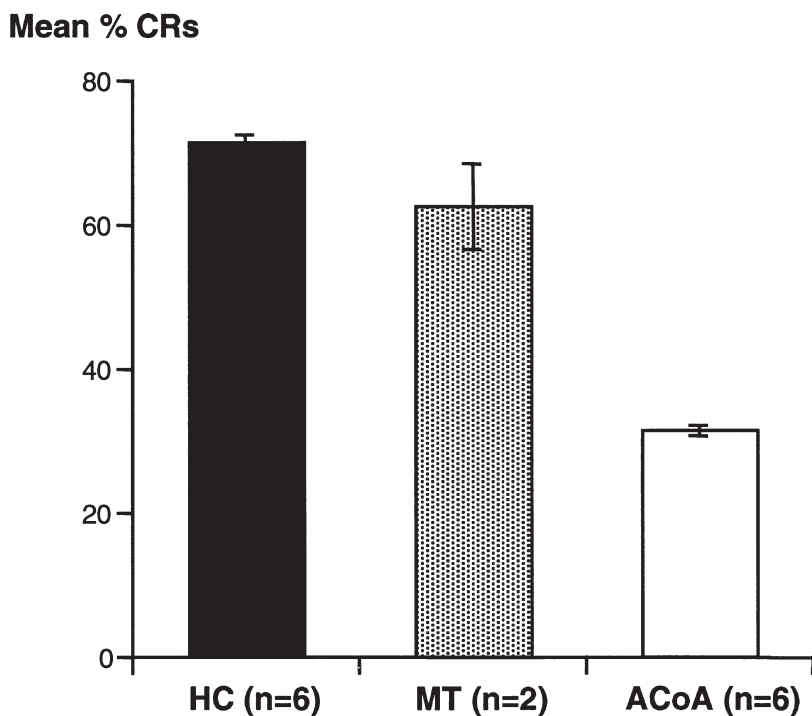


FIG. 4. Human delay eyeblink conditioning results. A group of individuals with basal forebrain amnesia subsequent to ACoA aneurysm rupture were significantly slower to condition than healthy control (HC) subjects (Myers, DeLuca et al., 2001). Two individuals with amnesia subsequent to etiologies that damage medial temporal (MT) areas did not condition significantly slower than controls.

By contrast, two individuals with amnesia due to etiologies that damage the medial temporal lobe conditioned at about the same rate as control subjects (Figure 4). Thus, it appears that human delay eyeblink conditioning shows the same pattern as in animals: impairment following basal forebrain damage but not following hippocampal damage. In the humans, like in the animals, it appeared that the impairment was not an inability to learn, but rather a general slowing of the rate at which the eyeblink response is acquired. Delay eyeblink conditioning, one of the simplest and most well-studied forms of associative learning, may therefore be sufficient to dissociate the learning impairments in medial temporal vs. basal forebrain amnesia.

### Extension to Other Forms of Simple Learning

The computational model predicts that this dissociation between the effects of hippocampal vs. basal forebrain damage (Figure 3B) should be a general effect, not limited to classical eyeblink conditioning. Thus, the model predicts that simple stimulus-response learning might survive hippocampal lesion but not hippocampal disruption, across a range of associative learning paradigms.

For example, Figure 5 shows a simple computer-based task in which subjects see two objects on the screen; each object has a distinct shape and color. A smiley face “reward” is hidden under one of the two objects. On the first trial, the computer raises the correct object to reveal the smiley face underneath; on subsequent trials, the subject must select



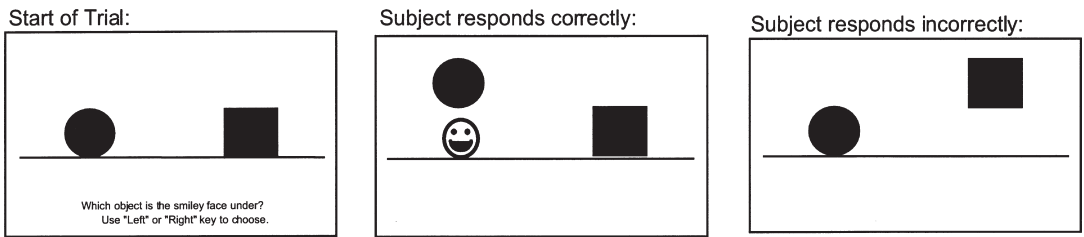


FIG 5. Screen events in the computer-based discrimination task. Subjects see two objects (left) and are asked to choose the left or right object; the chosen object is raised and, if the response was correct (center), a smiley face reward is revealed underneath. If incorrect (right), there is no smiley face.

the left or right object to find the smiley face. Trials are repeated, with the objects in random left-right arrangement, until the subject achieves a criterion of four consecutive correct responses.

Now, obviously, one way to approach this task is by simply memorizing the correct answer: in the example of Figure 5, choose the black circle and not the black square. This is a declarative solution that presumably depends on the medial temporal lobes. However, there is no *a priori* reason why the task could not be approached using non-declarative, incrementally-acquired, stimulus response associations: in effect, as a conditioned discrimination. Since individuals with medial temporal amnesia can learn conditioned discriminations in the eyeblink preparation (Daum, Channon & Gray, 1992), it seems reasonable that amnesics should be able to master this object discrimination task as well. In monkeys, hippocampal-region damage likewise spares 2-object discrimination (Zola-Morgan et al., 1992; Ridley et al., 1995).

However, just as medial septal damage disrupts the ability to learn simple CS-US associations in the eyeblink preparation, it ought to disrupt simple stimulus-response learning in the computer-based task. Specifically, basal forebrain amnesics should be slower to learn the correct response than control subjects, although with extended training they should be able to reach the same performance level as controls.

To test this prediction, we recently completed an initial study of four individuals with medial temporal amnesia (3 subsequent to hypoxia/anoxia, one subsequent to temporal lobe seizures) and four with basal forebrain amnesia subsequent to ACoA aneurysm rupture. Because the ACoA amnesics (mean age 63 years) were somewhat older than the MT amnesics (mean age 38 years), we recruited healthy controls matched to each patient group. Since the old and young controls did not differ from each other on any behavioral measures, these are combined into a single control group in the discussion and figures later.

Both amnesic groups were given a full battery of neuropsychological tests to assess memory and other cognitive function. Table 1 summarizes some key results. For example, the North American Adult Reading Test generates a VIQ measure assumed to index premorbid cognitive function; the VIQ is an age-adjusted measure with an expected mean of 100 and a standard deviation of 15 for healthy adults; the amnesic subjects all scored within the normal range on this measure and in fact the group means are slightly above normal. Similarly, the digit span (a subtest of the Wechsler Adult Intelligence Scale-Revised) provides a measure assumed to index attention; digit span scores for the two amnesic groups were not significantly different from those obtained by matched control subjects.

Subjects were also given tests of verbal and nonverbal memory, including the logical memory subtest of the Wechsler Memory Scale-Revised. In this test, the experimenter reads each of two paragraphs aloud; the subject must repeat the paragraphs from memory immediately and again after a 30-minute delay. Both amnesic groups scored significantly below controls on this task, with especially severe impairments on the delay portion. Importantly, the two amnesic groups did not differ from each other on any of these neuropsychological measures. In other words, based on standard neuropsychological assessment tools, there was no difference in impairment between the ACoA and MT amnesics.

On the computer-based task of Figure 5, all control and MT subjects completed the discrimination without any errors—i.e., they performed correctly from the very first trial. This is consistent with prior findings that MT amnesics are not impaired at learning a simple forced-choice discrimination between two objects (e.g., Reed & Squire, 1999, Phase 1). By contrast, the ACoA group required about five trials to reach criterion, and one ACoA subject failed to reach criterion within the maximum 12 trials. Figure 6A shows these data.

Thus, in this simple computer-based task, as in the delay eyeblink conditioning experiment, it appears that basal forebrain amnesia impairs learning the stimulus-response association, while medial temporal amnesia does not.

Once subjects had reached criterion performance in this computer-based discrimination task (stage 1), we added additional discrimination stages. Because prior studies had demonstrated that MT amnesics are impaired on learning multiple concurrent discriminations (e.g., Reed & Squire, 1999), we trained these additional discriminations progressively. First, we showed subjects a new discrimination pair and the correct answer; then trials with this new discrimination pair were intermixed with trials using the previously-trained discrimination pair, until subjects were performing correctly on both. A third discrimination was then added in the same way, and so on until subjects were trained to perform six discriminations concurrently (six stages total).

As Figure 6B shows, control subjects mastered the task easily; in fact, no control subject made more than a single error during the entire task. Three of the four MT amnesics likewise mastered all six discriminations; the fourth completed the first five stages but then failed to master the final discrimination within the maximum 72 trials. In the ACoA amnesic group, two subjects completed all six discriminations, while two completed stages 2–5 but failed to master the sixth (one of these was the one who had previously failed to master the first discrimination). A repeated-measures ANOVA confirmed significant effects of group ( $F(2, 13) = 4.30, p = .037$ ) and stage ( $F(5, 65) = 5.07, p = .001$ ) with a group-stage interaction ( $F(10, 65) = 2.03, p = .044$ ); post-hoc Tukey HSD tests confirmed that the ACoA group learned more slowly than controls or MT amnesics, particularly on the first stage of learning. Note that on stage 6, the relatively high average trials for the MT group is due to the single subject who failed to reach criterion in that stage; if that subject's data are deleted, the average for the remaining 3 MT subjects is a mere 2.33 trials, and the ACoA groups are again slower than control or MT groups.

These initial data suggest that the ACoA amnesics are impaired both on learning a single discrimination pair and on learning multiple concurrent discriminations. However, there appears to be little or no deficit in MT amnesics relative to control subjects.

### **Double Dissociation: Learning vs. Transfer**

The hippocampus may not be necessary for learning a single stimulus-response associa-

TABLE 1

Mean scores of ACoA and MT amnesic patient groups on selected neuropsychological tests; standard deviation in parentheses. Note two separate control groups were recruited, age matched to each patient group; control scores are averaged across both control groups.

	ACoA	MT	Control
Age (years)	62.8 (3.3)	38.3 (10.2)	50.5 (16.9)
VIQ	107.3 (2.3)	110.3 (10.6)	111.3 (11.4)
Digit Span	14.8 (2.2)	14.3 (5.0)	14.9 (1.5)
LM-immediate	18.0 (5.7)	14.0 (3.6)	28.0 (4.0) *
LM-delay	6.8 (3.6)	2.3 (2.6)	26.0 (4.0) *

\* = significant difference between control and both patient groups at the  $p < .05$  level.

tion, either in the delay eyeblink conditioning paradigm or in a computer-based discrimination task. However, if the task demands are made a little more complex, hippocampal involvement may be critical. For example, in the eyeblink conditioning paradigm, if contextual, configural or temporal information is required, animals with hippocampal-region damage are often profoundly impaired (e.g., Kim, Clark & Thompson, 1995; Port & Patterson, 1984; Shohamy, Allen & Gluck, 2000). Humans with MT amnesia are also impaired at conditioning tasks where temporal information is critical, such as the trace conditioning paradigm (e.g., McGlinchey-Berroth et al., 1997; Clark & Squire, 1998).

These principles appear to apply beyond eyeblink classical conditioning. For example, Howard Eichenbaum and colleagues have conducted a series of studies of odor discrimination in rats. They found that rats with hippocampal-region damage (fornix lesion) were not impaired at learning to discriminate two odors if the odors were presented separately, although they were impaired if the task was structured as a forced choice between two odors (Eichenbaum et al., 1988). More interestingly, the lesioned rats were severely impaired when familiar odor stimuli were presented as novel recombinations (Eichenbaum et al., 1989). For example, suppose that the task was to learn to prefer odor A over odor B, and to prefer odor C over odor D (Figure 7A). Once these discriminations were learned, rats were presented with a choice between odors A and D. Control rats reliably preferred the previously-reinforced odor A over odor D (Figure 7B). However, lesioned rats showed little preference for A—almost as if they failed to recognize A in the new context (Figure 7C).

One interpretation of this finding is that the lesioned rats tend to “overcompress” odor information, meaning that they perceive the odors as compounds AB and CD instead of learning about the component odors A, B, C, and D. One result of such overcompression is that, during the transfer phase, a novel pairing of familiar odors will be perceived as a new compound AD, about which nothing is known (Eichenbaum, Otto & Cohen, 1994; Myers & Gluck, 1996). Another way of stating the same general principle is to assume that the lesioned rats are “hyperspecific” in their learning, meaning that they learn how to respond

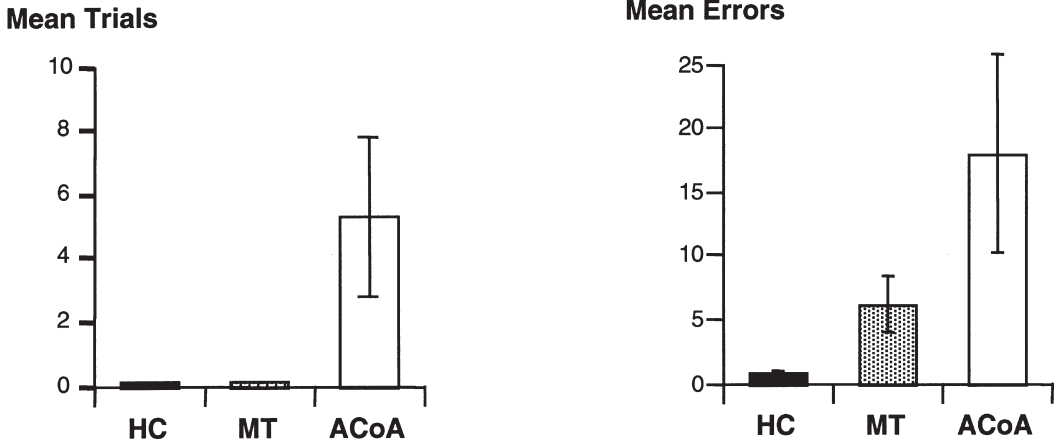
**(A) One Pair****(B) Six Pairs**

FIG. 6. Pilot results from the computer-based discrimination task. (A) On initial learning with one object pair, medial temporal (MT) amnesics learn as quickly as healthy controls (HC) while basal forebrain (ACoA) amnesics are significantly slower. (B) When the task is extended to include six discrimination pairs trained over successive stages, ACoA amnesics are still significantly slower than MT amnesics or controls.

to odor A in the context of odor B, but cannot generalize to respond to the same odor A when presented in the novel context of odor D. Similarly, human MT amnesics are often characterized as being “hyperspecific” in their learning, meaning that they are relatively unable to generalize when learned information is presented in new contexts (e.g., Schacter, 1985; Glisky, 1995).

Such an argument would predict that, even under those conditions where MT amnesics may be able to acquire simple stimulus-response associations, the MT amnesics will learn them in an overcompressed or hyperspecific way—and then be relatively unable to transfer when this familiar information is presented in a new way, just like the lesioned rats of Figure 7C.

Conversely, even though amnesics with basal forebrain damage may be slower to complete the initial stimulus-response learning, they should learn these associations in a manner that is not qualitatively different from controls, since their hippocampus is not disabled, only disrupted. For this reason, we predicted that ACoA amnesics would generally show good transfer when familiar information was presented in novel recombinations—more like the intact rats of Figure 7B.

To test this proposed double dissociation, we again considered our computer-based concurrent discrimination task. In each of the original trained pairs, the two objects differed in color or shape but not both. In the example of Figure 8A, the two objects differ in shape (circle vs. square) but not color (black). Since the color co-occurs, it is redundant with respect to predicting the smiley face location; shape alone is predictive.

Our computational model expects that the hippocampal region would tend to construct stimulus representations that compressed and even filtered out the redundant information, while differentiating and emphasizing the predictive information. Thus, in effect, associa-

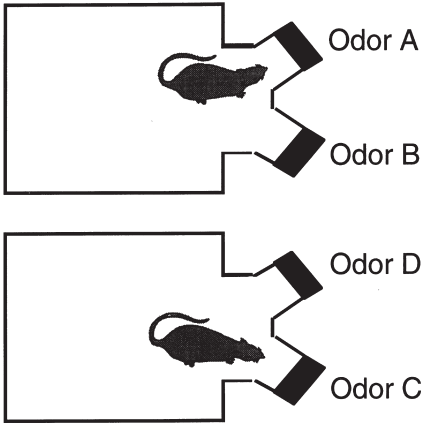
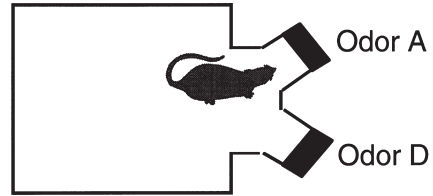
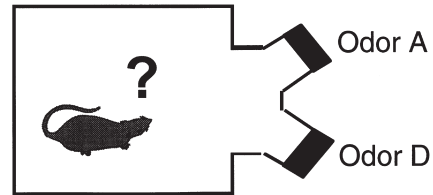
**(A) Initial Learning****(B) Transfer: Control Rats****(C) Transfer: Lesioned Rats**

FIG. 7. (A) Odor discrimination task in which rats are required to learn to prefer odor A over odor B and to prefer odor C over odor D. On a subsequent transfer phase in which familiar odors A and D are paired, control rats (B) reliably choose the previously-rewarded odor A; rats with hippocampal-region damage (C) show little preference for odor A, as if they do not recognize the familiar odors in their novel pairings (Eichenbaum et al., 1989).

tions are based on the predictive features (circle beats square) while redundant features are ignored. On the other hand, individuals lacking a hippocampal region would be unable to form such new representations, and would instead base their learning on the entire objects: black-circle beats black-square. Note that either strategy is perfectly adequate for mastering the discriminations, consistent with the finding (Figure 6A, 6B) that MT amnesics are not impaired at acquiring the task.

However, we followed the initial learning phase with a transfer phase, un signaled to the subject. The trials in the transfer were constructed so that the relevant features remained the same and only the irrelevant ones changed. So, whereas the first pair had initially been a black circle vs. a black square (Figure 8A), the transfer phase had the same shapes with different colors (Figure 8B). Now, the initial learning strategy becomes critical. If subjects had learned by basing associations on the predictive features (circle beats square), they should perform perfectly on the transfer phase, since the same features are still predictive. This is how we expected normal subjects to behave. However, if subjects had learned in a hyperspecific manner, basing associations on entire objects including both relevant and irrelevant features (black-circle beats black-square), they should perform very differently in the transfer phase. Specifically, the transfer phase objects should be treated as novel objects (gray-circle vs. gray-square) about which nothing is known, and performance should be close to chance. This is how we expected individuals with hippocampal-region damage to behave.

When our group of four MT amnesics was given this transfer test, they showed exactly

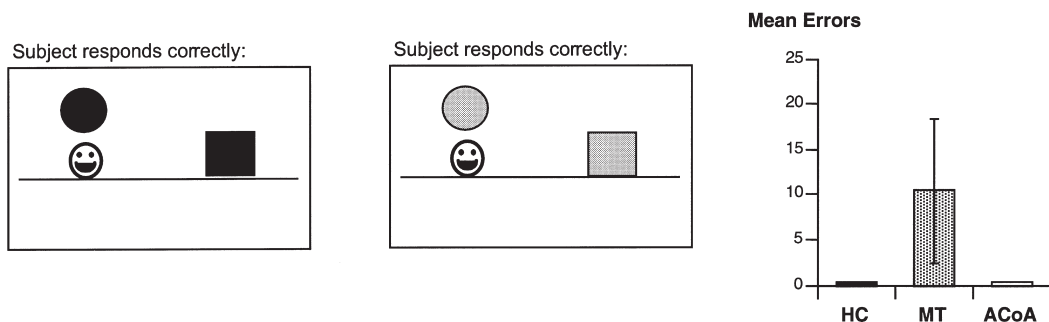
**(A) Initial Learning (B) Transfer Phase (C) Transfer Data**

FIG. 8. Computer-based transfer task. Phase 1 learning (A) is followed by a transfer phase (B) in which the relevant features remain the same but irrelevant features are changed. (C) On this transfer phase, MT amnesics show significantly more errors than controls, while ACoA amnesics transfer as well as controls.

this pattern. Although healthy controls transferred perfectly, the MT amnesics made significantly more errors before mastering the new discriminations (Figure 8C). This finding is consistent with a prior study showing that non-demented elderly with hippocampal atrophy learned the initial discriminations as quickly as non-atrophied counterparts, but were impaired at the transfer phase (Myers, Kluger et al., 2002).

In contrast, the ACoA amnesics, who had been slower to acquire the initial discriminations, transferred just as well as controls. This suggests that, even though individuals with basal forebrain amnesia may be slower to acquire initial stimulus-response learning, they do learn in a way that is qualitatively similar to controls, and are able to use this information flexibly in a transfer test.

The results in Figure 8C are pilot work based on a small number of subjects. Nevertheless, there appears to be a clear pattern: ACoA, but not MT, amnesia slows initial stimulus-response learning; conversely, MT, but not ACoA, amnesia impairs subsequent transfer. To our knowledge, this is the first time that a single task has been used to demonstrate a double dissociation between the learning impairments in MT vs. basal forebrain amnesia. Further, this double dissociation appears to be consistent with insights both from animal classical conditioning data and from computational models of the interaction between hippocampal-region and basal forebrain structures during learning.

### Conclusions and Open Questions

Several conclusions appear to emerge from the results discussed earlier. The first, and most obvious, is that human clinical studies may benefit from a better understanding of animal research and computational modeling. Principles that are clearly documented in animal data, such as the dissociation between the effects of hippocampal-region vs. basal forebrain damage on delay eyeblink conditioning, may apply to humans as well, and may help us to understand and differentiate the effects of such brain damage on humans.

In the case of human amnesia, the animal data suggest, and the pilot patient data appear to confirm, that the most interesting dissociations between medial temporal amnesia and

basal forebrain amnesia may lie not in the domain of declarative learning—which may be equally devastated in both etiologies—but in non-declarative learning, producing a subtle but distinctive pattern of impaired and spared abilities. If so, it is tempting to speculate about the degree to which such insights might have real-world application. Clearly, rehabilitation therapies for amnesia must make use of the forms of memory that may be relatively spared rather than those which are devastated. This in turn suggests that non-declarative techniques may be especially promising for further investigation.

Already, several studies have shown that non-declarative techniques can have some success at teaching new skills to amnesic patients (e.g., Glisky, Schacter & Tulving, 1986; Glisky, 1992, 1995; Van der Linden & Coyotte, 1995; Hirst et al., 1988). For example, Glisky and colleagues have conducted a series of studies using the method of “vanishing cues” (an implicit memory technique) to train amnesic individuals to perform computer data entry procedures (e.g., Glisky et al., 1986). The vanishing cues technique requires intensive long-term training, and the results are relatively specific, so that the patients may not transfer well when task demands change. Nevertheless, these studies suggest that non-declarative learning may be a useful place to begin developing targeted rehabilitation techniques for amnesia.

Further, the animal data suggest that there are important differences in the pattern of non-declarative learning abilities following damage to the hippocampal region vs. basal forebrain. Specifically, the animal data suggest that hippocampal-region damage may result in non-declarative learning that is fast but subsequently inflexible, while basal forebrain damage may result in slower non-declarative learning which is more amenable to generalization later. Our pilot data with the forced-choice computer task suggest that a parallel distinction between learning and transfer could be found in human amnesia.

In this context, it is suggestive to look at performance by individual amnesics in the vanishing cue studies. For example, while one amnesic with an etiology of encephalitis (usually associated with MT damage) required only 15 trials to reach criterion, compared with a mean of 19 trials for healthy controls, three ACoA amnesics required 79–198 trials (Glisky, 1992). Conversely, although most amnesics show limited generalization of this knowledge (e.g., Glisky et al., 1986), one patient with basal forebrain amnesia learned fairly slowly but then appeared to transfer this learning well from the laboratory to a home setting (Glisky, 1995). While caution is needed in drawing broad conclusions based on individual patient performance in a single-task domain, it appears that these data are consistent with a general pattern in which MT amnesia results in relative sparing of initial acquisition but devastated transfer, while basal forebrain amnesia results in slower initial learning but relatively spared transfer. Such a statement remains speculative at this point, but it is clear that insights from the animal literature can only improve our understanding of the amnesic syndrome in specific and the human brain in general.

## References

- Abe, K., Inokawa, M., Kashiwagi, A. & Yanagihara, T. (1998). Amnesia after a discrete basal forebrain lesion. *Journal of Neurology, Neurosurgery and Psychiatry*, *65*, 126–130.
- Akase, E., Alkon, D. L. & Disterhoft, J. F. (1989). Hippocampal lesions impair memory of short-delay conditioned eyeblink in rabbits. *Behavioral Neuroscience*, *103*(5), 935–943.
- Alexander, M. & Freedman, M. (1984). Amnesia after anterior communicating artery rupture. *Neurology*, *34*, 752–757.
- Allen, M., Myers, C. & Gluck, M. (2001). Parallel neural systems for classical conditioning: Support from computational modeling. *Integrative Physiological and Behavioral Science*, *36*, 36–61.

- Allen, M., Myers, C., Schnirman, G., Chelius, L., Masand, V. & Gluck, M. (2002). Learned irrelevance is a more robust pre-exposure effect than latent inhibition in eyeblink conditioning in both rabbit and human. Manuscript under editorial review.
- Berry, S. & Thompson, R. (1979). Medial septal lesions retard classical conditioning of the nictitating membrane response in rabbits. *Science*, *205*, 209–211.
- Blaxton, T., Zeffiro, T., Gabrieli, J., Bookheimer, S., Carrillo, M., Theodore, W. & Disterhoft, J. (1996). Functional mapping of human learning: A positron emission tomography study of eyeblink conditioning. *Journal of Neuroscience*, *16*, 4032–4040.
- Clark, R. & Squire, L. (1998). Classical conditioning and brain systems? The role of awareness. *Science*, *280*, 77–81.
- Damasio, A., Graff-Radford, N., Eslinger, P., Damasio, H. & Kassel, N. (1985). Amnesia following basal forebrain lesions. *Archives of Neurology*, *42*, 263–271.
- Daum, I., Channon, S. & Gray, J. (1992). Classical conditioning after temporal lobe lesions in man: Sparing of simple discrimination and extinction. *Behavioral Brain Research*, *52*, 159–165.
- Donegan, N. H., Gluck, M. A. & Thompson, R. F. (1989). Integrating behavioral and biological models of conditioning. In *Psychology of Learning and Motivation* (pp. 109–156). Academic Press.
- Eichenbaum, H., Fagan, A., Mathews, P. & Cohen, N. J. (1988). Hippocampal system dysfunction and odor discrimination learning in rats: Impairment or facilitation depending on representational demands. *Behavioral Neuroscience*, *102*, 331–339.
- Eichenbaum, H., Mathews, P. & Cohen, N. J. (1989). Further studies of hippocampal representation during odor discrimination learning. *Behavioral Neuroscience*, *103*, 1207–1216.
- Eichenbaum, H., Otto, T. & Cohen, N. (1994). Two functional components of the hippocampal memory system. *Behavioral and Brain Sciences*, *17*(3), 449–518.
- Everitt, B. & Robbins, T. (1997). Central cholinergic systems and cognition. *Annual Review of Psychology*, *48*, 649–684.
- Gabrieli, J., McGlinchey-Berroth, R., Carrillo, M., Gluck, M., Cermack, L. & Disterhoft, J. (1995). Intact delay-eyeblick classical conditioning in amnesia. *Behavioral Neuroscience*, *109*, 819–827.
- Gade, A. (1982). Amnesia after operations on aneurysms of the anterior communicating artery. *Surgical Neurology*, *18*, 46–69.
- Glisky, E. (1992). Acquisition and transfer of declarative and procedural knowledge by memory-impaired patients: A computer data-entry task. *Neuropsychologia*, *30*, 899–910.
- Glisky, E. (1995). Acquisition and transfer of word processing skill by an amnesic patient. *Neuropsychological Rehabilitation*, *5*, 299–318.
- Glisky, E., Schacter, D. & Tulving, E. (1986). Computer learning by memory-impaired patients: Acquisition and retention of computer knowledge. *Neuropsychologia*, *24*, 313–328.
- Gluck, M. & Bower, G. (1988). From conditioning to category learning: An adaptive network model. *Journal of Experimental Psychology: General*, *117*(3), 225–244.
- Gluck, M. & Myers, C. (1993). Hippocampal mediation of stimulus representation: A computational theory. *Hippocampus*, *3*, 491–516.
- Gluck, M. & Myers, C. (2001). *Gateway to Memory: An Introduction to Neural Network Modeling of the Hippocampus in Learning and Memory*. Cambridge, MA: MIT Press.
- Gluck, M., Myers, C. & Thompson, R. (1994). A computational model of the cerebellum and motor-reflex conditioning. In S. Zornetzer, J. Davis, C. Lau & T. McKenna (Eds.), *An Introduction to Neural and Electronic Networks* (pp. 91–98). New York: Academic Press.
- Gluck, M., Oliver, L. & Myers, C. (1996). Late-training amnesic deficits in probabilistic category learning: A neurocomputational analysis. *Learning and Memory*, *3*, 326–340.
- Gormezano, I., Kehoe, E. J. & Marshall, B. S. (1983). Twenty years of classical conditioning research with the rabbit. *Progress in Psychobiology and Physiological Psychology*, *10*, 197–275.
- Hasselmo, M. & Bower, J. (1993). Acetylcholine and memory. *Trends in Neurosciences*, *16*, 218–222.
- Hasselmo, M. & Schnell, E. (1994). Laminar selectivity of the cholinergic suppression of synaptic transmission in rat hippocampal region CA1: Computational modeling and brain slice physiology. *Journal of Neuroscience*, *14*, 3898–3914.
- Hasselmo, M. (1995). Neuromodulation and cortical function: Modeling the physiological basis of behavior. *Behavioural Brain Research*, *67*, 1–27.
- Hirst, W., Phelps, E., Johnson, M. & Volpe, B. (1988). Amnesia and second language learning. *Brain and Cognition*, *8*, 105–116.



- Kim, J., Clark, R. & Thompson, R. (1995). Hippocampectomy impairs the memory of recently, but not remotely, acquired trace eyeblink conditioned responses. *Behavioral Neuroscience*, *109*, 195–203.
- Kopelman, M. (1995). The Korsakoff syndrome. *British Journal of Psychiatry*, *166*, 154–173.
- Levy, W. B., Brassel, S. E. & Moore, S. D. (1983). Partial quantification of the associative synaptic learning rule of the dentate gyrus. *Neuroscience*, *8*, 799–808.
- Logan, C. & Grafton, S. (1995). Functional anatomy of human eyeblink conditioning determined with regional cerebral glucose metabolism and positron emission tomography. *Proceedings of the National Academy of Sciences, USA*, *92*, 7500–7504.
- McGlinchey-Berroth, R., Carrillo, M., Gabrieli, J., Brawn, C. & Disterhoft, J. (1997). Impaired trace eyeblink conditioning in bilateral medial-temporal lobe amnesia. *Behavioral Neuroscience*, *111*, 873–882.
- Morris, M., Bowers, D., Chatterjee, A. & Heilman, K. (1992). Amnesia following a discrete basal forebrain lesion. *Brain*, *115*, 1827–1847.
- Myers, C., DeLuca, J., Schultheis, M., Schnirman, G., Ermita, B., Diamond, B., Warren, S. & Gluck, M. (2001). Impaired delay eyeblink classical conditioning in individuals with anterograde amnesia resulting from anterior communicating artery aneurysm rupture. *Behavioral Neuroscience*, *115*, 560–570.
- Myers, C., Ermita, B., Harris, K., Hasselmo, M., Solomon, P. & Gluck, M. (1996). A computational model of the effects of septohippocampal disruption on classical eyeblink conditioning. *Neurobiology of Learning and Memory*, *66*, 51–66.
- Myers, C., Ermita, B., Hasselmo, M. & Gluck, M. (1998). Further implications of a computational model of septohippocampal cholinergic modulation in eyeblink conditioning. *Psychobiology*, *26*, 1–20.
- Myers, C. & Gluck, M. (1994). Context, conditioning and hippocampal re-representation. *Behavioral Neuroscience*, *108*, 835–847.
- Myers, C. & Gluck, M. (1996). Cortico-hippocampal representations in simultaneous odor discrimination learning: A computational interpretation of Eichenbaum, Mathews & Cohen (1989). *Behavioral Neuroscience*, *110*, 685–706.
- Myers, C., Kluger, A., Golomb, J., Ferris, S., de Leon, M., Schnirman, G. & Gluck, M. (2002). Hippocampal atrophy disrupts transfer generalization in non-demented elderly. *Journal of Geriatric Psychiatry and Neurology*, *15*(2), to appear.
- Myers, C., McGlinchey-Berroth, R., Warren, S., Monti, L., Brawn, C. & Gluck, M. (2000). Latent learning in medial temporal amnesia: Evidence for disrupted representational but preserved attentional processes. *Neuropsychology*, *14*, 3–15.
- Phillips, S., Sangalang, V. & Sterns, G. (1987). Basal forebrain infarction: A clinicopathologic correlation. *Archives of Neurology*, *44*, 1134–1138.
- Port, R. & Patterson, M. (1984). Fimbrial lesions and sensory preconditioning. *Behavioral Neuroscience*, *98*, 584–589.
- Reed, J. & Squire, L. (1999). Impaired transverse patterning in human amnesia is a special case of impaired memory for two-choice discrimination tasks. *Behavioral Neuroscience*, *113*, 3–9.
- Rescorla, R. & Wagner, A. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and non-reinforcement. In A. Black & W. Prokasy (Eds.), *Classical Conditioning II: Current Research and Theory* (pp. 64–99). New York: Appleton-Century-Crofts.
- Ridley, R., Timothy, C., Maclean, C. & Baker, H. (1995). Conditional learning and memory impairments following neurotoxic lesion of the CA1 field in hippocampus. *Neuroscience*, *67*, 263–275.
- Schacter, D. (1985). Multiple forms of memory in humans and animals. In N. Weinberger, J. McGaugh & G. Lynch (Eds.), *Memory Systems of the Brain: Animal and Human Cognitive Processes* (pp. 351–379). New York: Guildford Press.
- Schmajuk, N., Lam, Y. W. & Christiansen, B. (1994). Latent inhibition of the rat eyeblink response: Effect of hippocampal aspiration lesions. *Physiology and Behavior*, *55*, 597–601.
- Schmaltz, L. & Theios, J. (1972). Acquisition and extinction of a classically conditioned response in hippocampectomized rabbits (*Oryctolagus cuniculus*). *Journal of Comparative and Physiological Psychology*, *79*, 328–333.
- Shohamy, D., Allen, M. & Gluck, M. (2000). Dissociating entorhinal and hippocampal involvement in latent inhibition. *Behavioral Neuroscience*, *114*, 867–874.
- Solomon, P., Groccia-Ellison, M., Flynn, D., Mirak, J., Edwards, K., Duneheew, A. & Stanton, M. (1993). Disruption of human eyeblink conditioning after central cholinergic blockade with scopolamine. *Behavioral Neuroscience*, *107*, 271–279.
- Solomon, P., Lewis, J., LoTurco, J., Steinmetz, J. & Thompson, R. (1986). The role of the middle cerebral peduncle in acquisition and retention of the rabbit's classically conditioned nictitating membrane response. *Bulletin of the Psychonomic Society*, *24*, 75–78.

- Solomon, P. & Moore, J. (1975). Latent inhibition and stimulus generalization of the classically conditioned nictitating membrane response in rabbits (*Oryctolagus cuniculus*) following dorsal hippocampal ablation. *Journal of Comparative and Physiological Psychology*, *89*, 1192–1203.
- Solomon, P., Solomon, S., Van der Schaaf, E. & Perry, H. (1983). Altered activity in the hippocampus is more detrimental to classical conditioning than removing the structure. *Science*, *220*, 329–331.
- Squire, L. & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science*, *253*, 1380–1386.
- Stumpf, C., Petsche, H. & Gogolak, G. (1962). The significance of the rabbit's septum as a relay station between the midbrain and the hippocampus: II. The differential influence of drugs upon both cell firing patterns and the hippocampus theta activity. *Electroencephalography and Clinical Neurophysiology*, *14*, 212–219.
- Sutton, R. & Barto, A. (1981). Toward a modern theory of adaptive networks: Expectation and prediction. *Psychological Review*, *88*, 135–170.
- Thompson, R. (1986). The neurobiology of learning and memory. *Science*, *233*, 941–947.
- Van der Linden, M. & Coyette, F. (1995). Acquisition of word-processing knowledge in an amnesic patient: Implications for theory and rehabilitation. In R. Campbell & M. Conway (Eds.), *Broken Memories: Case Studies in Memory Impairments* (pp. 54–76). Cambridge, MA: Blackwell.
- Weiskrantz, L. & Warrington, E. (1979). Conditioning in amnesic patients. *Neuropsychologia*, *17*, 187–194.
- Widrow, B. & Hoff, M. (1960). Adaptive switching circuits. *Institute of Radio Engineers, Western Electronic Show and Convention Record*, *4*, 96–104.
- Woodruff-Pak, D. (1993). Eyeblink classical conditioning in HM: Delay and trace paradigms. *Behavioral neuroscience*, *107*, 911–925.
- Zola-Morgan, S., Squire, L., Rempel, N., Clower, R. & Amaral, D. (1992). Enduring memory impairment in monkeys after ischemic damage to the hippocampus. *Journal of Neuroscience*, *12*, 2582–2596.

