

# Dissociating Entorhinal and Hippocampal Involvement in Latent Inhibition

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This study used anatomical cues to suggest a functional dissociation between the roles of the entorhinal cortex and the hippocampus in learning. The authors proposed that the highly convergent inputs to the entorhinal cortex indicate this region may be particularly important for selecting or compressing information. This hypothesis was tested in rabbits (*Oryctolagus cuniculus*) trained on an associative learning task that is a common index of stimulus selection. In this task, known as latent inhibition, preexposure to a stimulus (such as a tone) leads to slowed learning when the same tone is subsequently paired with an outcome (such as an airpuff to the eye). As hypothesized, rabbits with neurotoxic lesions of the entorhinal cortex failed to show slowed learning following preexposure (no latent inhibition) and learned the association faster than control rabbits. In contrast, hippocampal-lesioned animals showed normal (slowed) learning.

The hippocampal region plays an important role in learning and memory. Studies in both humans and animals have demonstrated that damage to the hippocampal region results in a variety of learning and memory deficits, including anterograde amnesia (Squire, 1987), spatial-learning deficits (Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe & Nadel, 1978), and impairment on learning tasks requiring the use of configuration and context (Hirsh, 1974; Rudy & Sutherland, 1989, 1995). These findings have stimulated many different theories of hippocampal function (Buzsaki, 1989; Cohen & Eichenbaum, 1991; Gluck & Myers, 1993; O'Keefe & Nadel, 1978; Squire, 1987; Rudy & Sutherland, 1995). However, although each of these theories accounts for particular aspects of hippocampal region function, a comprehensive understanding of the role of this region in learning and memory remains elusive.

Part of the difficulty in gaining a comprehensive understanding of hippocampal function in learning may be attributed to the fact that many studies have treated the hippocampal region as a single functional unit. The hippocampal region, however, consists of several structures, including the dentate gyrus, hippocampal fields CA1 through CA4, the subicular complex, and the entorhinal cortex. These structures have distinct anatomical and physiological characteristics, suggesting that they are likely to have distinct functional contributions to the hippocampal learning system. Findings from recent lesion studies support this idea and demonstrate that behavioral functions that had previously been attributed to the hippocampal memory system as a whole are in fact associated with particular regions within the hippocampal system or with the cortices surrounding it (Good & Honey, 1997; Murray & Mishkin,

1996; Otto & Eichenbaum, 1992; Phillips & LeDoux, 1995; Suzuki, Zola-Morgan, Squire, & Amaral, 1993).

One structure within the hippocampal region that is of particular interest is the entorhinal cortex. The entorhinal cortex plays a key role in relaying information to the hippocampus. It serves as the primary source of polymodal sensory input to the hippocampus, receiving projections from a wide range of association cortices, including the adjacent perirhinal and parahippocampal cortices, and projecting this information to the hippocampus (Insausti, Amaral, & Cowan, 1987; Suzuki & Amaral, 1994a; Witter, Groenewegen, Silva, & Lohman, 1989). The entorhinal cortex also receives prominent feedback projections from the hippocampus, which are in turn sent back to the same association cortices from which the input originated. Thus, the entorhinal cortex serves as an important interface between the hippocampus and the neocortex (Van Hoesen, 1982).

There are several lines of evidence indicating that the entorhinal cortex is not merely a relay for sensory information but rather that it contributes directly to learning and memory function. For example, neurons in the entorhinal cortex have been shown to display stimulus-specific activity that is modified by an animal's experience with that stimulus (Young, Otto, Fox, & Eichenbaum, 1997; Zhu & Brown, 1995; Zhu, Brown, & Aggleton, 1995), and damage to the entorhinal cortex is implicated in several human pathologies associated with cognitive deficits including Alzheimer's dementia (Hyman, Van Hoesen, & Damasio, 1990), temporal lobe epilepsy (Du et al., 1993), and schizophrenia (Arnold, Hyman, Van Hoesen, & Damasio, 1991). Animal-lesion studies have also found that damage that includes the entorhinal cortex leads to memory impairments that are more severe than those caused by selective lesions of the hippocampus alone (e.g., Eichenbaum, Otto, & Cohen, 1994; Jarrard, 1993; Zola-Morgan, Squire, Rempel, Clower, & Amaral, 1992). However, because most of these studies involved lesions to several structures in addition to the entorhinal cortex (such as the adjacent perirhinal and parahippocampal cortices), they have not yielded a clear understanding of precisely what the functional role of the entorhinal cortex may be.

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Anatomical studies also suggest that the entorhinal cortex has a functional contribution to the hippocampal memory system. It has been demonstrated in both humans and animals that the wide range of neocortical inputs to the entorhinal cortex are highly convergent, synapsing onto a relatively small number of neurons in Layers II and III of the entorhinal cortex (Suzuki & Amaral, 1994b). This suggests that the entorhinal cortex may play an important role in selecting or compressing cortical information before transmitting this information to the hippocampus. Results from the limited number of studies that have examined the behavioral effects of damage solely to the entorhinal cortex are generally consistent with this idea (e.g., Freeman, Weible, Rossi, & Gabriel, 1997; Maren & Fanselow, 1997). However, most of these studies used nonselective lesion techniques (such as aspiration or electrolytic) that are known to create damage extending beyond the entorhinal cortex (Jarrard, 1989), making it very difficult to specify the selective contribution of the entorhinal cortex to these tasks. Furthermore, although many of the tasks studied are likely to involve selection or compression of stimuli, none of these studies have examined this capacity directly.

Consistent with the anatomical data, Myers, Gluck, and Granger (1995) have suggested that the entorhinal cortex may play a role in compression of stimulus-stimulus and stimulus-outcome representations during associative learning. The key idea is that when two stimuli are repeatedly presented together, the entorhinal cortex may serve to create a compressed representation of the two stimuli. This compression results in increased generalization between the two stimuli when they are subsequently encountered. Eichenbaum et al. (1994) have also proposed a similar role for the parahippocampal region (which includes the entorhinal, perirhinal, and parahippocampal cortices), suggesting that it may mediate "fusion" of cooccurring or nearly coincidental stimuli (Bunsey & Eichenbaum, 1993).

One conditioning paradigm that is thought to involve such a process of stimulus compression is latent inhibition. In latent inhibition, repeated nonreinforced preexposure to a conditioned stimulus (CS) normally slows conditioning to that stimulus when it is subsequently paired with a reinforcer (or unconditioned stimulus [US]; Lubow, 1973). Thus, latent inhibition is a form of stimulus selection that allows efficient learning to those stimuli that are behaviorally significant while suppressing learning to those stimuli that are irrelevant. Latent inhibition is a very robust effect that has been demonstrated in a variety of species and with a wide variety of learning paradigms (see Lubow, 1997, for review). The role of stimulus compression in latent inhibition is thought to be important during the preexposure phase because the cooccurrence of the context and the CS would lead to a compressed representation of the stimulus and the context. Thus, in subsequent learning, when the CS comes to predict the US but the context does not, it is necessary to differentiate from the compressed representation to learn the association between the CS and the US.

The role of the hippocampal region in latent inhibition is not entirely clear. Although numerous studies have addressed this question, they have yielded inconsistent and contradicting results. Part of the reason for this inconsistency is that the particular effect of stimulus preexposure differs depending on the particular latent inhibition design (within-subject or between-subjects) and the particular paradigm and stimuli used, such as food-cup, taste-

aversion, or eyeblink conditioning (Buhusi, Gray, & Schmajuk, 1998). Another important source of inconsistency is the use of different lesions in the various studies. Early lesion studies, using nonselective lesion techniques, have shown that damage to the hippocampal region disrupts the latent inhibition effect (e.g., Ackil, Mellgren, Halgren, & Frommer, 1969; Schmajuk, Lam, & Christiansen, 1994; Solomon & Moore, 1975), leading researchers to conclude that the hippocampus plays an important role in stimulus selection. However, this claim has been challenged, as later studies using more selective neurotoxic lesions of the hippocampus were not able to replicate earlier results (Honey & Good, 1993; Reilly, Harley, & Revusky, 1993), suggesting that other structures in the hippocampal region, and not the hippocampus itself, are likely to be involved (however, note Han, Gallagher, & Holland, 1995, for the opposite effect with a within-subject appetitive task). These data, in conjunction with the anatomical and behavioral data implicating involvement of the entorhinal cortex in compressing stimulus representation, suggest that the entorhinal cortex may play an important role in mediating the preexposure effects of latent inhibition.

The goal of the present study was to explore the role of the entorhinal cortex in stimulus compression and to examine the selective contribution of the entorhinal cortex, as dissociated from the hippocampus proper, in a latent inhibition paradigm of eyeblink conditioning. In eyeblink conditioning, subjects are repeatedly presented with a corneal airpuff US, which is always immediately preceded by a tone CS. After repeated CS-US pairings, subjects learn to generate an anticipatory blink response (conditioned response [CR]) when they hear the tone, so that eyelid closure occurs at the expected airpuff times. The eyeblink conditioning procedure was chosen for this study because it has proven to be particularly useful for demonstrating latent inhibition in both humans and animals (e.g., Schnur and Ksir, 1969; Solomon & Moore, 1975) and because the neural substrates for acquisition of the basic CS-US association in this procedure are well-understood and do not rely on the hippocampal region (McCormick & Thompson, 1984), thus ensuring that any effects are due to processes related to the preexposure itself and not to the basic acquisition.

Ibotenic acid was used to create selective neurotoxic lesions of the entorhinal cortex or the dorsal hippocampus in the rabbit, and the effect of stimulus preexposure on subsequent learning was examined. The involvement of the entorhinal cortex in latent inhibition was determined by comparing the effect of CS preexposure on subsequent learning in rabbits with entorhinal cortex lesions with the same effect in sham-operated control rabbits and in hippocampal-lesioned rabbits. The purpose of the hippocampal lesion group was twofold: First, because the entorhinal cortex is the main source of input to the hippocampus, it was necessary to verify that any effect of entorhinal cortex lesions on learning was due to the loss of entorhinal function itself and not due to loss of hippocampal input. Second, it was hoped that a direct comparison of the effect of the two types of selective lesions, within a single latent inhibition paradigm, might help clarify the role of the hippocampus in latent inhibition. It was expected, first, that entorhinal cortex lesions would disrupt latent inhibition so that preexposed or non-preexposed entorhinal-lesioned animals would learn at the same rate. Second, it was expected that selective hippocampal lesions would not disrupt latent inhibition, so that hippocampal-lesioned animals that were preexposed to the cue

would condition more slowly than those that were not preexposed. Third, it was expected that overall, because of the disruption of latent inhibition in entorhinal-lesioned animals, the entorhinal cortex lesion would in fact lead to faster learning and to higher levels of conditioning than in the sham-lesioned or hippocampal-lesioned preexposed groups.

## Method

### Subjects

Subjects were 42 male New Zealand albino rabbits (*Oryctolagus cuniculus*; Covance Laboratories, Philadelphia), weighing 2.3–2.7 kg at the time of surgery. Rabbits were randomly distributed among the six experimental groups, with seven rabbits in each group: entorhinal-cortex-lesioned preexposed, entorhinal cortex non-preexposed, hippocampal-lesioned preexposed, hippocampal non-preexposed, sham-lesioned preexposed, and sham non-preexposed. Rabbits were individually housed with ad lib access to food and water and were maintained on 12-hr light–dark cycles.

### Surgery

Before surgery, rabbits were weighed, and a baseline respiration rate was taken. Rabbits were then given a subcutaneous injection of xylazine (6.0 mg/kg). Fifteen minutes later, rabbits were anesthetized with an intramuscular injection of ketamine (60.0 mg/kg), followed 15 min later by a 1-cc intramuscular injection of ketamine/xylazine mixture (2:1) and placed in a stereotaxic frame (Kopf Instruments, Tujunga, CA). This injection was repeated hourly until the end of the surgical procedure. The head was shaved and scrubbed with a betadine scrub, followed by isopropyl alcohol and betadine preparatory solution.

Each rabbit was placed in a standard stereotaxic head holder (Kopf Instruments). The head was leveled so that lambda was 1.5 mm lower than bregma. A 30-gauge cannula connected to a 10- $\mu$ l Hamilton microsyringe was lowered through a small hole in the skull to the lesion site. Ibotenic acid (10  $\mu$ g/ $\mu$ l; Sigma Laboratories, St. Louis, MO) was bilaterally injected into 12 injection sites for the entorhinal cortex lesions and 24 injection sites for the dorsal hippocampal lesions. Coordinates and injection volumes are presented in Table 1. For each injection site, the injection cannula was left in place for 1 min before the injection was started,

Table 1  
Stereotaxic Coordinates for Entorhinal Cortex  
and Hippocampal Lesions

Lesion site	Coordinate (mm)			Volume of ibotenic injection ( $\mu$ l)
	AP	ML	DV	
Entorhinal cortex	-5.0	$\pm$ 5.5	-19, -20	2.0
	-5.0	$\pm$ 6.2	-19, -20	2.0
	-5.0	$\pm$ 7.5	-19, -20	1.0
Dorsal hippocampus	-4.0	$\pm$ 3.0	-5.2, -3.2*	1.5 or 1.0
	-4.0	$\pm$ 5.0	-5.2*, -3.2	1.5 or 1.0
	-5.0	$\pm$ 4.0	-5.2, -3.2*	1.5 or 1.0
	-5.0	$\pm$ 7.5	-5.7*, -3.5	1.5 or 1.0
	-6.0	$\pm$ 4.5	-5.5, -3.8*	1.5 or 1.0
	-6.0	$\pm$ 8.0	-6.5*, -4.2	1.5 or 1.0

Note. Bregma was used for the zero point for the anterior–posterior (AP) and midline (ML) coordinates, and the dorsoventral (DV) measure was taken from the surface of dura. The volume of injection for the hippocampal lesion was 1.5 or 1.0  $\mu$ l per site; asterisks indicate which DV coordinate received the 1.0- $\mu$ l injection.

injections took place over 2 min, and the cannula was left in place for another 2 min after the injection was finished.

Once injections were completed, the holes in the skull were covered with bone wax, holes for skull screws were drilled, and skull screws were inserted. Dental acrylic was applied to cover exposed skull, and a small bolt was mounted for use during behavioral training (to mount eyeblink and air hose assembly). Rabbits were allowed to recover to full consciousness and put back in the home cage.

Rabbits in the sham-surgery condition underwent the same surgical procedures with the exception that no injections were made. Following surgery, rabbits recovered for 1 week before behavioral training was initiated.

### Apparatus

The apparatus consisted of individual chambers with a speaker that produced a tone of 90 dB (on the wall facing the rabbit) and a fan for circulation of air and generation of background white noise of 75 dB (on the opposite wall). An infrared eyeblink detector and airpuff jet were attached to headgear and were connected to an interface board (Keithley Metrabyte, Taunton, MA) that contained a microprocessor. The interface board interacted with an IBM PC computer with software written in the C programming language that controlled stimulus presentation and behavioral response recording (for technical details of eyeblink detectors, see Thompson, Moyer, Akase, & Disterhoft, 1994). The computer controlled an interface board that was a digital/analog–analog/digital converter and triggered a set of relays gating the tone CS and the airpuff US presentations. The eyeblink detector air hose assembly was mounted on a bolt on the headstage of the rabbit, such that the detector was placed immediately adjacent to the right eye of the rabbit. The voltage from the infrared device was amplified and differentiated; eyelid movement data were transferred to the computer for analysis and storage.

### Training Procedures

Before behavioral training, all rabbits were habituated to the behavioral apparatus. Rabbits were placed in a Plexiglas restraint box located inside the conditioning chamber. On the 1st day of habituation, rabbits were placed in the restraint box for a time equivalent to half a session. On the 2nd day of adaptation, rabbits were placed in the chamber for the full length of a training session, with the eyeblink detector mounted. Training began on the 3rd day. Each session of behavioral training consisted of 100 trials. Rabbits in the preexposure group received 850 trials of the CS alone over eight-and-a-half daily sessions. So that rabbits in the non-preexposure group would receive equivalent amounts of exposure to the conditioning context, they received 850 blank trials with no stimuli presented over eight-and-a-half daily sessions. On the 9th day of preexposure, all rabbits received 50 blank trials followed immediately by 50 training trials. Training trials consisted of forward-paired presentations of the CS (a 450-ms, 1000-Hz, 95-dB tone), which coterminated with the US (a 50-ms, 3-psi corneal airpuff). The variable intertrial interval averaged 25–30 ms.

### Behavioral Assessment

Eyeblink closures were detected by disruptions in the reflected infrared light and amplified and recorded by a specialized data-acquisition board and personal computer. Eye closure with an amplitude greater than 0.5 was defined as an eyeblink. An eyeblink in the period following US onset was considered to be an unconditioned response (UR) occurring as a reflex in response to the arrival of the airpuff. Eyeblinks occurring before tone onset or within the first 100 ms of tone presentation were considered to be spontaneous blinks. Only responses occurring during the CS period (100–399 ms) were considered to be learned CRs. On each trial, the computer

program reported whether a CR occurred, the CR amplitude, the UR amplitude, and the latency for blink onset and peak amplitude of the blink.

### Histology

After completion of behavioral testing, the rabbits were killed by overdose of an IV injection of pentobarbital into the marginal ear vein and perfused through the ascending aorta with 1 L (0.9% [wt/vol]) saline solution followed by 1 L (10% [vol/vol]) formaline solution. Brains were removed and stored in a 10% (vol/vol) formaline–30% (vol/vol) sucrose solution for approximately 1 week. Coronal sections of the brain were then taken in a cryostat (80 microns thick), mounted on slides, and Nissl stained. Histological examination was performed with the aid of the Urban and Richard (1972) stereotaxic atlas of the rabbit brain.

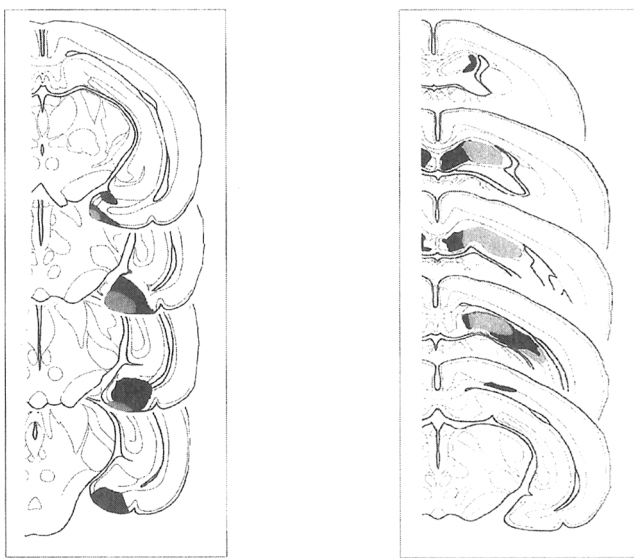
### Data Analysis

A repeated measures analysis of variance (ANOVA) was used to compare the percentage of CR across training trials in the different groups included in this study (entorhinal-lesioned preexposed, entorhinal-lesioned non-preexposed, hippocampal-lesioned preexposed, hippocampal-lesioned non-preexposed, sham-lesioned preexposed, and sham-lesioned non-preexposed). A specific comparison was planned to contrast learning in those groups expected to learn relatively fast (sham-lesioned non-preexposed, hippocampal-lesioned non-preexposed, entorhinal-lesioned non-preexposed, and entorhinal-lesioned preexposed) with those groups expected to learn more slowly because of the inhibitory effects of preexposure (sham-lesioned and hippocampal-lesioned preexposed).

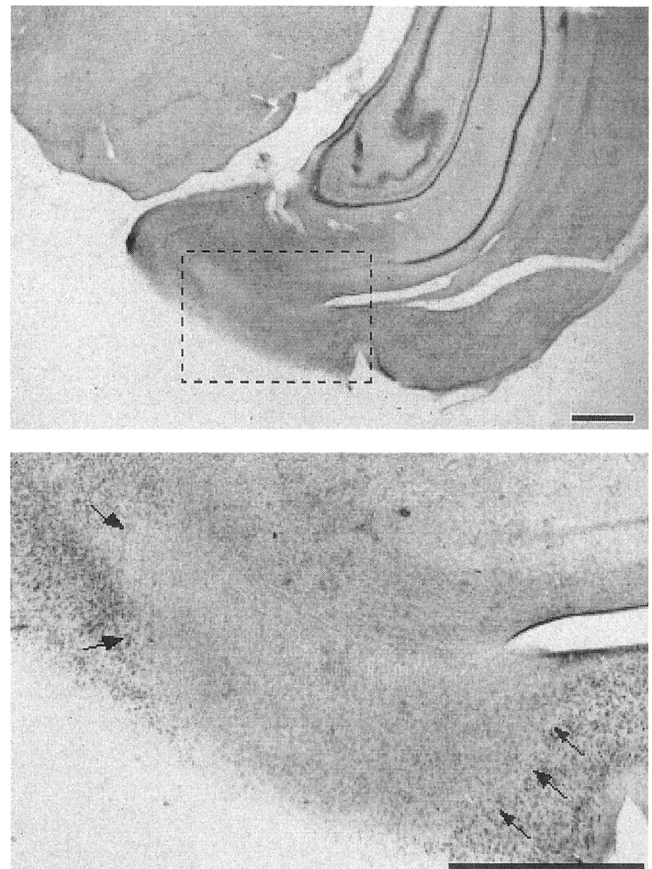
## Results

### Histology

Histological analysis of rabbits with lesions revealed that in most cases of entorhinal cortex lesions, a significant portion of the entorhinal cortex cell field, focusing around the medial portion, was damaged. One of the entorhinal-lesioned rabbits (non-preexposed) had some damage extending into the ventral hippocampus. Figure 1



*Figure 1.* Serial sections illustrating the extent of maximal (black) and minimal (gray) lesions of the entorhinal cortex (left) and the hippocampus (right). Sections are from rostral (top) to caudal (bottom).



*Figure 2.* Photomicrographs of a representative lesion of the entorhinal cortex. Bottom photo shows enlargement of framed region in the top. Arrows indicate the regions of cell loss. Bars represent 1 mm.

(left) illustrates the extent of maximal and minimal damage for the entorhinal cortex lesions. Figure 2 shows a photomicrograph of a typical entorhinal cortex lesion. For the hippocampal lesions, the histological analysis revealed that the dorsal hippocampal cell field was almost entirely damaged in most cases. Lesions were highly consistent between subjects. In three cases (one preexposed, two non-preexposed), the lesions were inconsistent with the rest of the rabbits and extended beyond the dorsal hippocampus. These subjects were removed from further analyses. Figure 1 (right) illustrates the extent of maximal and minimal damage for the hippocampal lesions. Figure 3 shows a photomicrograph of a typical hippocampal lesion.

### Behavioral Data

After excluding 3 rabbits on the basis of histological results and 2 rabbits because of death (1 entorhinal non-preexposed) and equipment failures (1 sham preexposed), behavioral analyses were performed for the 37 rabbits that remained in the study (7 entorhinal-cortex-lesioned preexposed, 6 entorhinal cortex non-preexposed, 6 hippocampal-lesioned preexposed, 5 hippocampal non-preexposed, 6 sham-lesioned preexposed, and 7 sham non-preexposed).

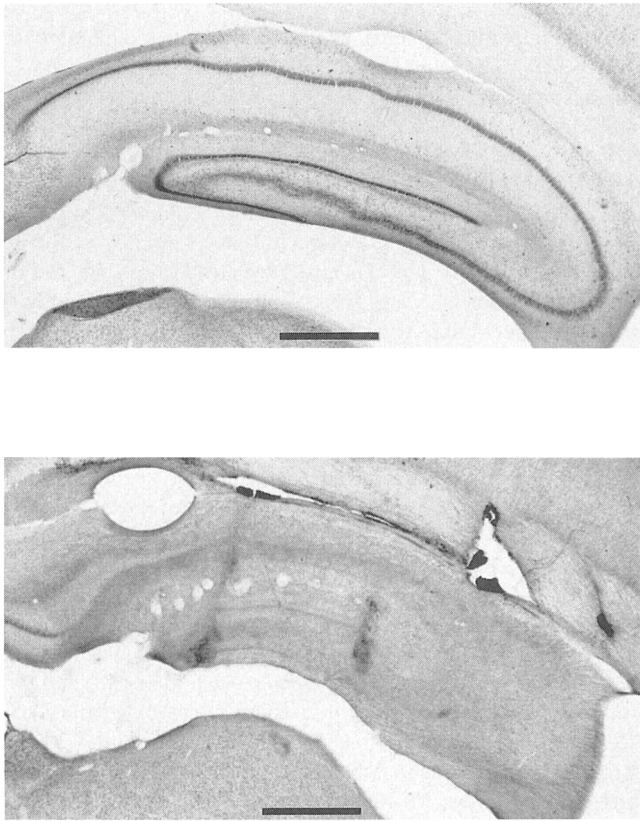


Figure 3. Photomicrographs of a representative lesion of the dorsal hippocampus. Top: intact hippocampus in a control rabbit. Bottom: dorsal hippocampus in a lesioned rabbit. Bars represent 1 mm.

A repeated measures ANOVA run on all six groups indicated a significant main effect of learning across blocks,  $F(12, 372) = 87.46, p < .001$ . A preplanned comparison of the groups indicated that overall, the sham-lesioned and hippocampal-lesioned preexposed rabbits were significantly slower than the sham- and hippocampal-lesioned non-preexposed and the entorhinal-lesioned preexposed and non-preexposed groups, as expected,  $F(1, 31) = 9.25, p < .01$ . These effects are illustrated in Figure 4, which shows conditioned eyeblink responding to the tone during the acquisition phase for each of the groups. Figure 4A depicts the latent inhibition effect in sham-lesioned rabbits, with slower learning in the preexposed group as compared with the non-preexposed group. A similar effect was found among the hippocampal-lesioned rabbits, as shown in Figure 4B, but this effect was abolished by entorhinal cortex lesions, as shown in Figure 4C. Overall, the entorhinal-lesioned rabbits that were preexposed to the tone learned faster than both the sham- and the hippocampal-lesioned rabbits, as shown in Figure 5.

Discussion

The purpose of this study was to examine the role of the entorhinal cortex in learning using the latent inhibition paradigm. The results demonstrate that, among rabbits with entorhinal cortex lesions, preexposure to a tone had no effect on subsequent learning

of an association between the tone and an airpuff. This is indicated by the similar levels of conditioned responding apparent between the preexposed and the non-preexposed entorhinal-lesioned subjects. In fact, entorhinal-lesioned rabbits learned faster than other

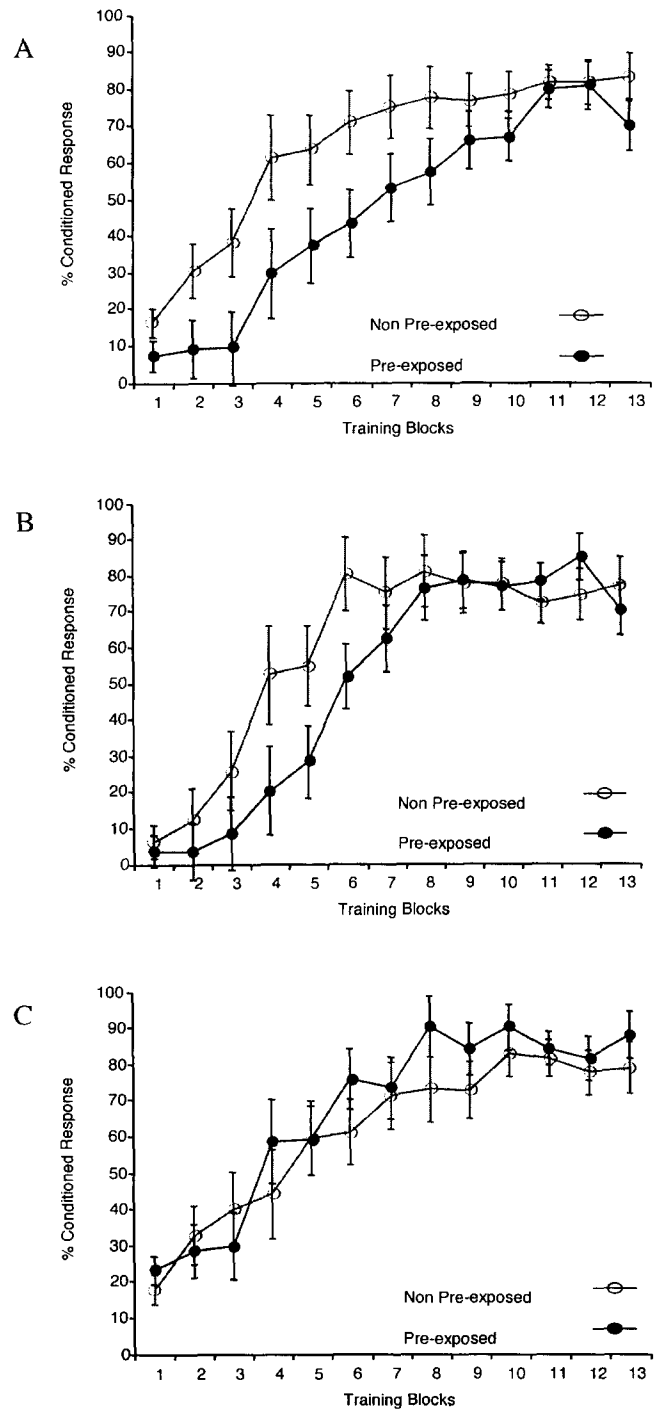


Figure 4. Acquisition of conditioned eyeblink response to the tone conditioned stimulus throughout training for the sham-lesioned (A), hippocampal-lesioned (B), and entorhinal-lesioned (C) groups. Error bars represent SE above and below the mean.

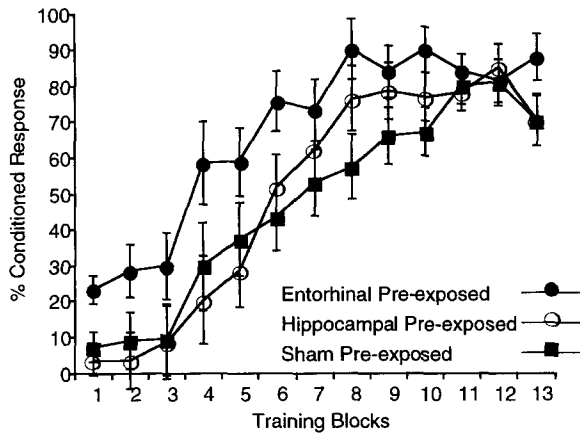


Figure 5. Acquisition of conditioned eyeblink response to the tone conditioned stimulus throughout training for the three preexposed groups. Error bars represent *SE* above and below the mean.

lesioned preexposed groups, as shown in Figure 5. These findings are consistent with our hypothesis that the entorhinal cortex plays an important role in mediating the preexposure effects of latent inhibition by compressing stimulus–context representation.

#### *Dissociating Entorhinal and Hippocampal Function*

Given the key role of the entorhinal cortex as an interface between neocortex and the hippocampus, one could argue that the effect of entorhinal cortex lesions observed here is not due to loss of entorhinal function in and of itself. Rather, the effect could be due to loss of input from the entorhinal cortex to the hippocampus. However, if this were the case, selective hippocampal lesions should also have resulted in a disruption of latent inhibition. Instead, we found a clear dissociation between the effect of entorhinal and hippocampal lesions: Entorhinal cortex lesions disrupted latent inhibition, whereas selective hippocampal lesions did not, suggesting that the entorhinal cortex itself is importantly involved in mediating the preexposure effects of latent inhibition. Furthermore, these effects are most likely not due to differences in lesion size, because the entorhinal cortex lesions were in fact less complete and damaged proportionally fewer entorhinal cells than did the hippocampal lesions. Taken together, these findings suggest a dissociation between hippocampal function and entorhinal cortex function in learning.

#### *Latent Inhibition and the Hippocampus*

The finding that the entorhinal cortex, but not the hippocampus, is critically involved in mediating the preexposure effects of latent inhibition is consistent with previous studies showing that selective hippocampal lesions do not disrupt latent inhibition in rats (Honey & Good, 1993), whereas nonselective broad hippocampal-region lesions (Coutureau, Galani, Gosselin, Majchrzak, & Di Scala, 1999; Kaye & Pearce, 1987; Schmajuk et al., 1994; Solomon & Moore, 1975) and parahippocampal lesions do (Yee, Feldon, & Rawlins, 1995). These results suggest that the attenuated latent inhibition found with broad and nonselective hippocampal lesions may in fact have been a result of entorhinal cortex

damage. However, it appears that lesion size is not the only factor that determines hippocampal involvement in latent inhibition, because Han et al. (1995) found that selective neurotoxic dorsal hippocampal lesions did attenuate latent inhibition, a finding which appears to be in contradiction to the present results. Although the precise reason for this discrepancy is not entirely clear, it most likely indicates that the specific paradigm and experimental design are critical factors for determining the importance of hippocampal involvement in the task, as discussed recently by Buhusi et al. (1998). Specifically, Han et al. used an appetitive preparation and a within-subject design, whereas we used eyeblink conditioning in a between-subjects design. It appears that the within- versus between-subjects design, rather than the preparation, may be the critical difference between the results of these two studies, because other studies examining the effect of selective hippocampal lesions have all used between-subjects designs (including an appetitive paradigm) and did not find an attenuation of latent inhibition (Honey & Good, 1993) or even found an enhanced effect (Reilly et al., 1993).

The main difference between the within-subject and between-subjects designs is in the conditioning phase of the experiment. In both designs, the preexposure phase consists of repeated presentation of a cue with no consequence. However, whereas the between-subjects design then compares conditioning to the same stimulus when it is paired with a consequence to learning in a second group that was not preexposed, the within-subject design compares conditioning to two alternating stimuli: one CS that was preexposed and one CS that was novel. These two conditioning procedures are likely to involve different representational processes. For example, the alternated presentation of the two CSs may lead to increased novelty, which in turn has been shown to decrease latent inhibition (Buhusi, Gray, & Schmajuk, 1998). Furthermore, the presentation of two CSs that predict the same consequence may lead to increased overlap in the representation of the two stimuli. Taken together, these results suggest that the hippocampus may be highly important for precisely those conditioning processes that distinguish between these two types of studies, because hippocampal lesions have such a disruptive effect on one but no effect on the other. This suggests that although the entorhinal cortex may be importantly involved in the preexposure effects of latent inhibition, the hippocampus may be particularly involved in the conditioning phase. These effects should be explored more directly in future studies.

#### *Entorhinal Cortex Involvement in Other Learning Paradigms*

We have presented data showing that entorhinal cortex lesions abolish latent inhibition, whereas hippocampal lesions do not. These results are consistent with our hypothesis regarding the role of the entorhinal cortex in compression of stimulus representations during learning. However, future studies are needed to examine the role of the entorhinal cortex in other learning paradigms that are likely to involve similar processes of stimulus compression. One such study found a similar effect of selective hippocampal and entorhinal lesions on a preexposure learning paradigm termed *learned irrelevance* (Allen, Chelius, & Gluck, 1998). Learned irrelevance is similar to latent inhibition in that subjects are preexposed to cues and are subsequently conditioned using the same

cues. The main difference between the two paradigms is that in latent inhibition subjects are exposed to only the CS, whereas in learned irrelevance subjects are exposed to deliberately unpaired presentations of the CS and the US. As in latent inhibition, this preexposure normally leads to slower learning in the conditioning phase when the CS and US are paired (Allen et al., 1998; Baker, 1976). In support of the hypothesized role of the entorhinal cortex in compressing stimulus representation, Allen et al. (1998) found that selective entorhinal cortex lesions disrupted the learned irrelevance effect, whereas hippocampal lesions did not.

### Conclusions

In summary, the present findings suggest that the entorhinal cortex may normally mediate associative learning tasks such as latent inhibition. Furthermore, these results suggest a dissociation between the functional contributions of the hippocampus and the entorhinal cortex for at least some types of associative learning tasks. Further investigation, primarily focusing on other learning paradigms and other stimuli, is necessary to provide a clearer understanding of the role of the entorhinal cortex in learning. However, in conjunction with previous anatomical and behavioral reports, these results provide evidence that the entorhinal cortex may play an important role in modulating stimulus representation. Dissociating the functional contribution of the entorhinal cortex and the hippocampus, as well as of other structures within the hippocampal region memory system, has important theoretical implications for understanding the role of the hippocampal memory system as a whole.

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