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Research report

# Lesions of the perirhinal cortex impair sensory preconditioning in rats

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**Abstract**

The effects of lesions of the perirhinal cortex on the development of associations between two conditioned stimuli (CSs) were examined with a sensory preconditioning procedure. Rats were given either bilateral electrolytic lesions of the perirhinal cortex or control surgery. They were then given either paired or unpaired presentations of a light CS and a tone CS. All of the rats were then given eyeblink conditioning procedures that involved paired presentations of either the light or tone and a periorbital shock unconditioned stimulus (US). The rats were finally given a test session that consisted of unpaired presentations of the tone and light CSs. Sensory preconditioning was established in the control group, but not in the lesion group. The findings are consistent with the view that the perirhinal cortex is involved in forming associations between neutral stimuli (even in the absence of reinforcement). 

*Keywords:* Rhinal; Learning; Eye-blink; Perirhinal; Conditioning; Associative

## 1. Introduction

A great deal of progress has been made toward understanding the neurobiology of simple associative learning [1,9,11,16,19,24–26,29,39,42,49]. Classical conditioning procedures can be used to establish simple associative learning by pairing a conditioned stimulus (CS) with an unconditioned stimulus (US). Sensory preconditioning is a special case of simple associative learning because it involves an initial pairing of two conditioned stimuli (CS1 and CS2 in phase 1) in the absence of an unconditioned stimulus, after which the subject is trained in traditional classical conditioning (CS1-US in phase 2) [5]. The presence of an association between CS1 and CS2 can only be inferred by post-training test presentations of CS2 (phase 3). Previous studies have shown that animals given initial CS1-CS2 pairings before CS1-US training respond to test presentations of CS2, whereas control groups given unpaired presentations of CS1 and CS2 do not [36,37,47,48]. It is thought that the animals given paired training respond to CS2 by virtue of its association with the excitatory CS1 [5,48]. The two conditioned stimuli often differ in modality (e.g. tone and light) and thus require the formation of a crossmodal association.

It is difficult to specifically distinguish between disruptions of encoding or retrieval because of their intimate relationship [38,50]. However, the clearly delineated encoding and retrieval opportunities for a CS1-CS2 association in sensory preconditioning (i.e. phase 1 and phase 3, respectively) enable a more focused study of the underlying neural bases of sensory associations.

Previous studies of the neural mechanisms of sensory preconditioning demonstrated that lesions of non-specific association cortex [47], the fimbria [36], or field CA1 of the hippocampus [37] prevented the establishment of sensory preconditioning. Based on these studies, a reasonable conclusion is that the connectivity between the hippocampus and cerebral cortex must

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remain intact for sensory preconditioning to be established.

The cortical areas surrounding the hippocampus in the rat have been divided into postrhinal, perirhinal, and entorhinal cortices [8]. The perirhinal and postrhinal cortices both provide input to the entorhinal cortex. However, in the rat, the perirhinal cortex receives substantial input from both auditory and visual cortical areas, whereas the postrhinal cortex receives input primarily from visual cortex [7,10]. This connectivity establishes the perirhinal cortex as a major source of polysensory information for the subiculum and hippocampus via substantial connections with the lateral entorhinal cortex [8,32,40]. Thus, the perirhinal efferents to the hippocampus may provide the necessary information for crossmodal sensory associations. There is precedence for the view that the hippocampus and parahippocampal region constitute functionally distinct components of a larger system [6,12–14,33,43] or are components of overlapping, but separate systems [15,20–22,28,30,35,51].

It has recently been proposed that the parahippocampal region binds the elements of paired associates, whereas the relations among the paired elements are dependent on hippocampal processing [12]. In context of sensory preconditioning, it is possible that the perirhinal cortex functions in the encoding or storage of the CS1-CS2 association, which is flexibly expressed by the paired group in the testing phase.

The current study used a sensory preconditioning procedure to examine the role of the perirhinal cortex in the development of associations between two conditioned stimuli. Rats were given either bilateral lesions of the perirhinal cortex or control surgery followed one week later by three phases of training. In Phase 1, half of the rats from each surgical group were given paired presentations of a tone CS and a light CS. The other half of the rats were given unpaired presentations of the two CSs. In Phase 2, all of the rats were given eyeblink conditioning procedures that involved paired presentations of either the light or tone and a periorbital shock US. In Phase 3, all of the rats were given a test session that consisted of unpaired presentations of the tone and light CSs (Table 1).

Table 1

| Training condition | Phase 1[a,b] | Phase 2[a,b] | Phase 3[a,b] |
|---|---|---|---|
| SPC | TL− | T+ or L+ | T−, L− |
| CNTL | T−, L− | T+ or L+ | T−, L− |

[a] T, indicates a tone conditioned stimulus and L indicates a light conditioned stimulus.

[b] +, indicates that the US was presented and − indicates that the US was not presented.

## 2. Materials and methods

### 2.1. Subjects

Subjects were 27 male Long–Evans rats (200–250 g). The rats were housed in the animal colony in Spence Laboratories at the University of Iowa. All rats were maintained on a 12-h light, 12-h dark photoperiod, with light onset at 06:30 h. The rats were assigned to one of two surgical groups (control or lesion) and one of two training conditions (paired or unpaired, see Section 2.4 below).

### 2.2. Surgery

One week prior to training, rats were removed from their home cage and anesthetized by an i.p. injection of sodium pentobarbital (60 mg/kg). Upon the onset of anesthesia, the rats were fitted with differential EMG electrodes that were implanted in the left upper eyelid muscles (orbicularis oculi) and a ground electrode was attached to a stainless steel skull screw. The EMG electrode leads terminated in gold pins in a plastic connector, which was secured to the skull with dental acrylic. A bipolar stimulating electrode (for delivering the shock US) was implanted subdermally, immediately caudal to the left eye. The bipolar electrode terminated in a plastic connector that was secured to the skull by dental acrylic.

Three electrolytic lesions were made in each hemisphere using procedures similar to the methods used by Wiig and Burwell [52]. The coordinates for the skull holes were 3.3, 4.8, and 6.3 mm posterior to bregma and 4.8 lateral to the midline. Insulated stainless steel electrodes were oriented laterally at 10° from vertical and lowered to 7.2 mm below the skull surface. In the lesion group, 1.0 mA of DC current was applied for 10 s at each lesion site. In the control group, the lesioning electrodes were lowered to the same coordinates, but no current was passed. The surgical site was closed with sutures on both sides of the electrode connectors. The connectors for the EMG electrodes and bipolar stimulating electrode were connected to lightweight cables that allowed the rats to move freely during conditioning.

### 2.3. Conditioning apparatus

The conditioning apparatus consisted of four small-animal sound attenuation chamber (BRS/LVE, Laurel, MD). Within each sound attenuation chamber was a small-animal operant chamber (BRS/LVE, Laurel, MD) where the rats were kept during conditioning. One wall of the operant chamber was fitted with two speakers that independently produce tones of up to 120 db SPL, with a frequency range of approximately 1000–

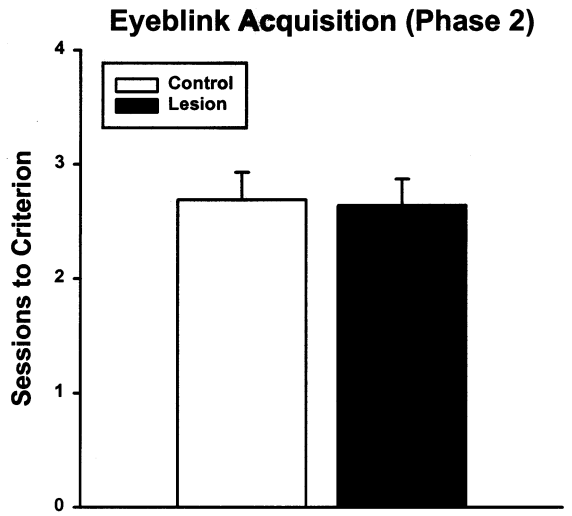


Fig. 1. Mean (SEM) sessions to reach criterion in the control (white bar) and lesion (black bar) surgical groups during training phase 2.

9000 Hz. The back wall of the sound attenuating chamber was equipped with a small light. The electrode leads from the rat's headstage were connected to peripheral equipment and a computer. Computer software controlled the delivery of stimuli and the recording of eyelid EMG activity. One circuit permitted the delivery of a shock stimulus (1–2 mA, DC constant current) through a stimulus isolator (Model number 365A, World Precision Instruments, Sarasota, FL). EMG activity was recorded differentially, filtered, amplified, rectified, and integrated by equipment that was similar to that used in previous studies [17,44].

### 2.4. Conditioning procedure

The rats were given three phases of training (Table 1). During phase 1, the rats in the paired condition were presented with a 400 ms tone (2.0 kHz, 85 dB) that was paired with a 400 ms light stimulus for ten trials. The rats in the unpaired condition were given explicitly unpaired presentations of the tone and light stimuli. Immediately preceding phase 1 training, all rats were pre-exposed to the conditioning chamber for 15 min. During phase 2, all of the rats were given 100 paired presentations of either the tone or light CS and a 25 ms periorbital shock (1–2.0 mA) US. The CS and US coterminated, yielding an interstimulus interval of 375 ms. Each rat was trained until it reached a performance criterion of 80% CRs during a session. During phase 3, all of the rats were given unpaired presentations of the tone and light CSs in an irregular sequence. The US was not presented during phase 3. Conditioned responses (CRs) were defined as responses that crossed a threshold 0.4 units (amplified and integrated arbitrary units) above baseline during the CS period but before the onset of the US. Unconditioned responses (URs) were defined as responses that crossed the threshold after the onset of the US [17,44]. During phase 3, CRs were defined as responses that crossed the threshold during the period between CS-onset and the end of the trial (700 ms).

### 2.5. Histology

On the day after training, the rats were euthanized with a lethal injection of sodium pentobarbital (90 mg/kg) and transcardially perfused with physiological saline followed by 3% formalin. After perfusion, the brains were post-fixed in the same fixative, and subsequently sectioned at 50 μm with a sliding microtome. Sections were then stained with cresyl violet. The location and extent of the lesions were determined by examination of serial sections.

## 3. Results

### 3.1. Behaviour

The rats did not exhibit CRs during the first phase of training. All rats used in this study reached the performance criterion of 80% CRs during training phase 2 (Fig. 1). Sensory preconditioning was evident in the rats given control surgery, but not in the rats given lesions of the perirhinal cortex. As Fig. 2 shows, control rats given paired presentations of the tone and light in phase 1 responded to the non-reinforced stimulus (CS2) more than control rats given unpaired presentations of the tone and light in phase 1. Fig. 2 also shows that this difference was not present in the lesion group. During the test session, the percentage of CRs during presentations of the non-reinforced CS (CS2) was greater in the control group given paired training than in the other three groups (i.e. control-unpaired, lesion-paired, and lesion unpaired). The percentage of CRs to the non-reinforced CS2 did not differ between the lesion-paired and lesion-unpaired groups. There were no spontaneous eyelid responses recorded during the pre-CS baseline periods. It is therefore likely that the low levels of responding to the CS2 in the control-unpaired, lesion paired, and lesion unpaired groups were due to generalization. There were no group differences in the percentage of CRs exhibited during trials in which the reinforced CS (CS1) was presented.

The relative rates of responding to the non-reinforced CS2 during the test session were also examined due to apparent differences in the rates of extinction between groups. The relative rates of responding were determined by dividing the percentage of CRs to the non-reinforced CS2 by the total percentage of CRs. The relative rate of responding to the non-reinforced CS2 was greater in the control-paired group than in the

other three groups (Fig. 3). Moreover, the relative rates of responding for the lesion-paired and lesion-unpaired groups did not differ.

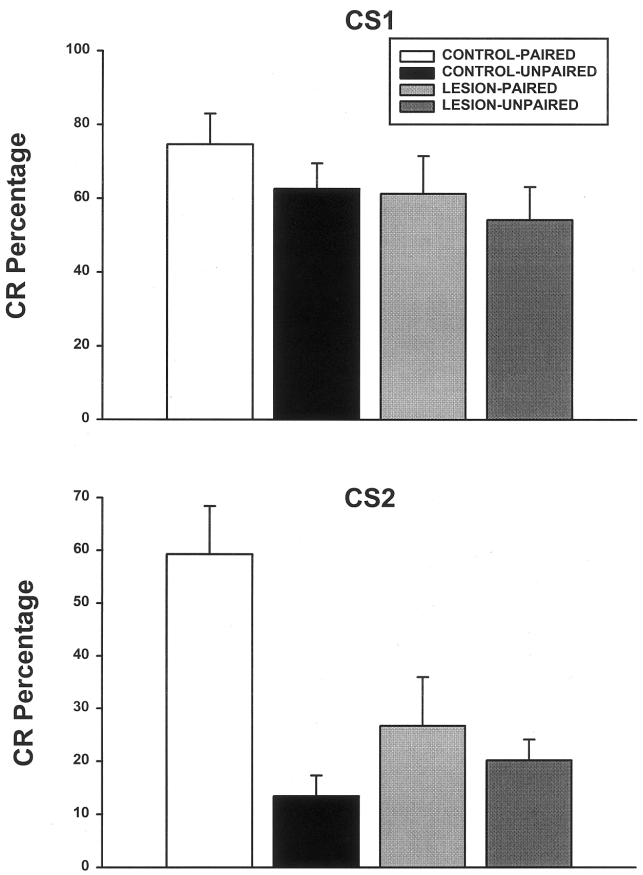


Fig. 2. Mean (SEM) percentage of conditioned responses on trials with presentations of the reinforced CS1 (upper panel) or the non-reinforced CS2 (lower panel) for the control-paired (white bar), control-unpaired (black bar), lesion-paired (light gray), and lesion-unpaired (dark gray) groups during the test session (training phase 3).

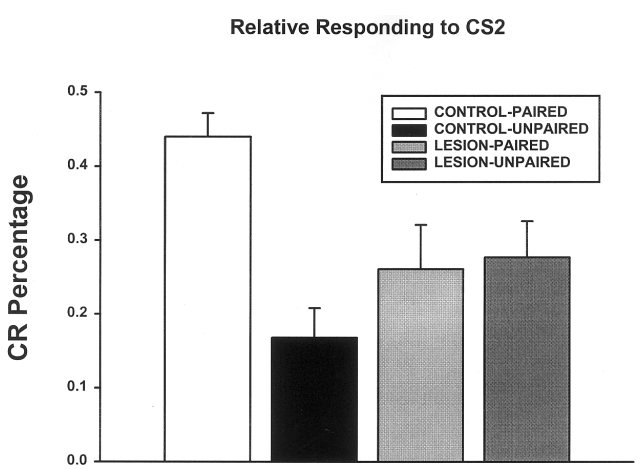


Fig. 3. Mean (SEM) proportion of conditioned responses to presentations of the non-reinforced CS2 for the control-paired (white bar), control-unpaired (black bar), lesion-paired (light gray), and lesion-unpaired (dark gray) groups during the test session (training phase 3).

The findings were examined statistically by ANOVA. The analysis of the test session data yielded significant effects involving the group (control vs. lesion surgery) and condition (paired vs. unpaired training) factors for absolute responding to the non-reinforced CS2 ($F(1, 23) = 8.09$, $P < 0.01$) and the relative rates of responding to the non-reinforced CS2 ($F(1, 23) = 8.74$, $P < 0.008$). There were no significant group or condition effects for CR performance during trials in which the reinforced stimulus (CS1) was presented. Post-hoc tests (Tukey's HSD) of the absolute and relative percentage of CRs exhibited during the trials with the non-reinforced CS2 revealed significantly greater responding in the control-paired group relative to the other three groups (all comparisons, $P < 0.05$). In addition, the absolute and relative percentage of CRs to the non-reinforced CS2 did not differ between the lesion-paired and lesion-unpaired groups.

### 3.2. Lesions

All rats in the lesion group sustained bilateral damage to the perirhinal cortex (range 18–81%) (Fig. 4). There were no differences in the extent of the lesion between paired and unpaired groups. The majority of the rats sustained damage to the most lateral portions of the lateral entorhinal cortex. Two animals sustained very minor unilateral damage ($< 0.5$ mm$^3$) to area CA1 of the hippocampus. A regression analysis found no significant relationship between lesion size and relative rate of responding ($r_{x,y} = -0.202$) in the lesion-paired group. Damage to fibers of passage by the electrolytic lesions was unlikely due to the low density of myelinated fibers in the perirhinal cortex [52]. Indeed, across the lesion group, the only pattern of damage related to performance was bilateral damage to the perirhinal cortex. Most lesions spared dorsal portions of area 36. To the extent that area 35 and area 36 may subserve different functions within the perirhinal cortex [8], it is interesting to note that all effective lesions included substantial damage to area 35. Rats with damage in the auditory cortex were not used in the data analysis.

## 4. Discussion

The present study investigated the effects of lesions of the perirhinal cortex on the formation of associations between two conditioned stimuli using a sensory preconditioning procedure. Sensory preconditioning was established in the control group receiving initial paired presentations of CS1 and CS2. Sensory preconditioning was not established in either lesion group nor in the control group receiving initial unpaired presentations of CS1 and CS2.

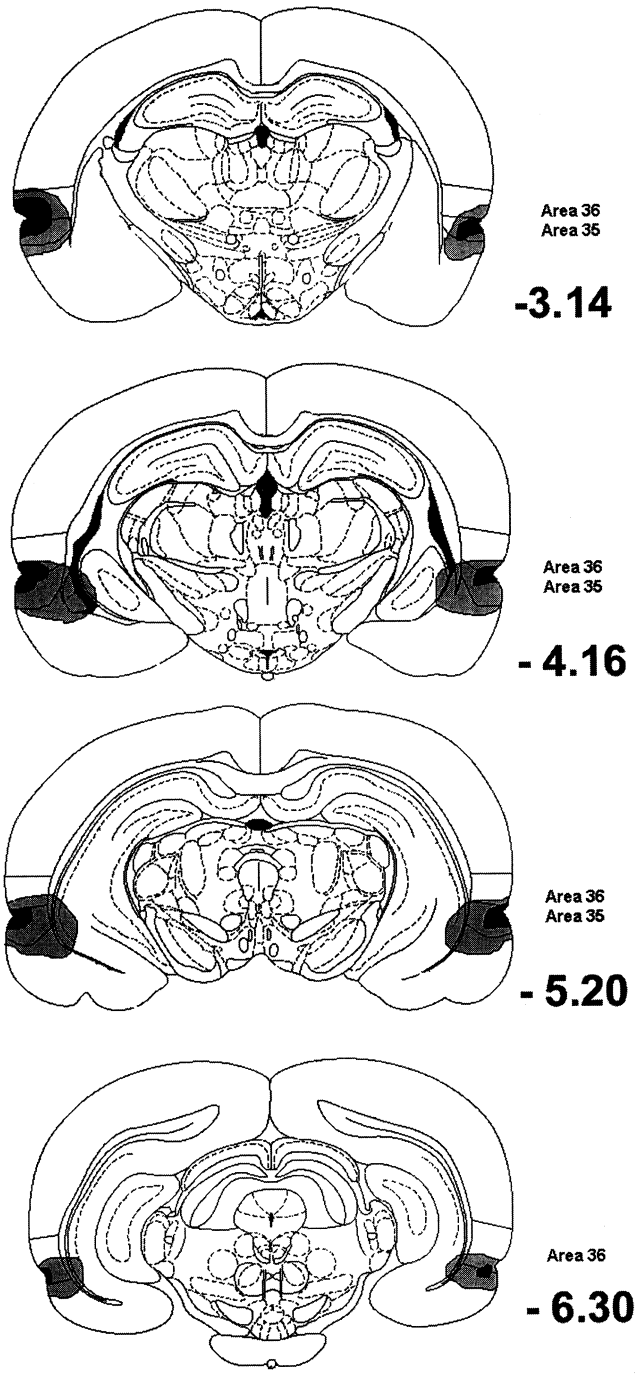


Fig. 4. Drawings of four coronal sections of the rat brain from the most rostral (top) to the most caudal (bottom) section. The smallest (blackened regions) and largest lesions (shaded regions) are depicted. The values to the right of each section indicate the stereotaxic coordinates relative to bregma [34]. The boundaries for the perirhinal cortex (Brodmann's area 35 and area 36) are adapted from Burwell and Amaral [7,8].

There are at least three possible roles for the perirhinal cortex in sensory preconditioning. First, the perirhinal cortex may provide the hippocampus with specific sensory information about the CSs. Investigations of the cortical afferents of the rat perirhinal cortex have reported that it receives substantial unimodal and polymodal cortical input [7,10]. Importantly, the rat perirhinal cortex could provide information to the hippocampus via substantial connectivity with the entorhinal cortex [8,32,40]. Damage to the perirhinal cortex would have indirectly impaired sensory preconditioning by denying the hippocampus and/or entorhinal cortex information that is essential for making associations between CS1 and CS2. Thus, the perirhinal cortex may be a temporary store or relay of elemental and/or crossmodal sensory representations [14]. Second, the perirhinal cortex may be responsible for encoding associations in the first two phases of sensory preconditioning. Lesioning the perirhinal cortex may have prevented cortical encoding of the associations in training (e.g. CS1-CS2 and CS1-US) [31], but did not affect acquisition of delay eyeblink conditioning because this form of conditioning requires only brainstem and cerebellar circuitry [27,49]. The third possibility is that the perirhinal cortex may store the individual associations formed in the first two phases of sensory preconditioning, e.g. CS1-CS2 and CS1-US. Lesions of the perirhinal cortex may have prevented the storage of these associations, which precluded their accessibility to the hippocampus. Accordingly, the function of the perirhinal cortex may be as an intermediate-term store of sensory associations [12,28,52].

It is clear that the perirhinal cortex and/or hippocampus must somehow interact with the brainstem and cerebellar circuitry to influence the eyeblink response. It is likely that the hippocampus first influences the cingulate cortex, and that the cingulate cortex and thalamus directly modify the eyeblink circuitry. Gabriel and colleagues have demonstrated that the hippocampal system modulates cingulate cortical and limbic thalamic areas via excitatory input from the subiculum [18,23]. Berger [4] first proposed a multi-synaptic pathway whereby the hippocampus and its projections to the retrosplenial cortex could provide the cerebellum with task-relevant information via retrosplenial cortical projections to the pontine nuclei. Moreover, two recent studies have reported the presence of excitatory corticopontine synapses from the prefrontal cortex in rats [2] and the posterior cingulate cortex in rabbits [3]. These findings suggest that the hippocampal projections to both the cingulate gyrus and retrosplenial cortex could provide input to the pontine nuclei. The pontine nuclear projections are the primary source of conditioned stimulus information to the cerebellum [41,45,46]. Consequently, limbic circuitry may modify pontine nuclear afferents to the cerebellar cortex and deep nuclei.

In conclusion, the results of the present experiment provide more evidence for the role of the perirhinal cortex in learning and memory. The results are consistent with some of the current views of the role of the medial temporal lobe system in memory [12,43]. In

particular, the present demonstration that lesions of the perirhinal cortex impair sensory preconditioning is consistent with the view that the medial temporal lobe system forms arbitrary associations in memory [12–14]. However, further studies are necessary to provide a detailed account of the role of the perirhinal cortex in forming associations between sensory stimuli in the absence of reinforcement and/or the flexible use of associative information in sensory preconditioning.

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