Lesions of the Fornix but Not the Entorhinal or Perirhinal Cortex Interfere with Contextual Fear Conditioning

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The effects of entorhinal cortex lesions, combined entorhinal and perirhinal cortex lesions, and fornix lesions on the conditioning of fear responses (freezing) to contextual stimuli were examined using a conditioning procedure known to produce hippocampal-dependent contextual conditioning. Lesions of the entorhinal and or entorhinal plus perirhinal cortex did not disrupt contextual conditioning, but lesions of the fornix did. None of the lesions affected conditioning to an explicit conditioned stimulus. Given that the entorhinal cortex is the primary linkage between the neocortex and the hippocampus and that the fornix is the primary linkage with subcortical structures, subcortical inputs to and outputs of the hippocampus appear to be sufficient to mediate contextual fear conditioning. As a result, the presumption that neocortical information is required for contextual fear conditioning, and perhaps other hippocampal-dependent functions, should be reevaluated.

[Key words: context, fear conditioning, memory, hippocampus, entorhinal cortex, fornix]

Recent studies have implicated the hippocampal formation as an essential component of the circuitry through which contextual stimuli acquire aversive properties through fear conditioning (Selden et al., 1991; Kim and Fanselow, 1992, 1993; Phillips and LeDoux, 1992, 1994). It is generally assumed that hippocampal-dependent functions involve the prior processing of sensory information in cortical areas, relay to multimodal processing regions in the parahippocampal region, transmission to the entorhinal cortex, and finally, entry into hippocampal circuitry (Van Hoesen et al., 1972; Swanson and Kohler, 1986; Deacon et al., 1988; Amaral and Witter, 1989). By this logic, damage to the entorhinal cortex should interfere with performance on hippocampal dependent tasks, as the entorhinal cortex is a critical link between the neocortex and the hippocampus, both providing the hippocampus with neocortical inputs and providing the neocortex with hippocampal outputs. Damage to the entorhinal cortex has, in fact, been found to interfere with performance on a number of hippocampal-dependent tasks (Murray et al., 1989; Zola-Morgan et al., 1989; Bunsey and Eichenbaum, 1993; Mumby and Pinel, 1994; Nagahara et al., 1995), but the effects of

entorhinal cortex lesions have not been examined in contextual fear conditioning.

In the present study we therefore examined the effects of lesions of entorhinal cortex on contextual fear conditioning. Our failure to find an effect prompted us to perform three additional studies. First, we examined the effect of combined lesions of the entorhinal cortex and perirhinal cortex, since the latter is also known to receive inputs from cortical sensory processing areas and project directly to the hippocampal formation and the amygdala (Deacon et al., 1983; Turner and Zimmer, 1984; McDonald and Jackson, 1987; Burwell and Amaral, 1993; Romanski and LeDoux, 1993). Connections with the amygdala are of interest since it is an essential component in the fear conditioning circuitry (Davis, 1992; Kapp, 1992; LeDoux, 1992, 1995). Second, we examined the effects of damage to the fornix, which constitutes another main source of input and output connections of the hippocampus (Swanson and Cowan, 1977; Amaral, 1987; Amaral and Witter, 1989). Third, in order to verify that our entorhinal cortex lesions interfered with hippocampal functions that are dependent on the entorhinal cortex, animals with entorhinal cortex lesions were tested on a passive avoidance task, known to be disrupted by manipulations of either the entorhinal cortex (Izquierdo et al., 1993) or the hippocampus (O'Keefe and Nadel, 1978; Gray, 1982).

Materials and Method

Animals and surgery. Male Sprague–Dawley rats (Hilltop labs), which weighed 250–275 gm upon arrival, were housed in pairs in clear plastic cages. They were provided with free access to lab chow and water and maintained on a 12 hr:12 hr light–dark cycle.

About 7 d after arrival, animals in the entorhinal cortex lesion group (Ent, $n = 8$) were anesthetized with pentobarbital (40 mg/kg) and mounted in a custom made head holding device. The cranium was exposed and a craniotomy was performed over the posterior cortex. Entorhinal cortex lesions were made by visualizing the rhinal sinus, retracting the dura and slowly aspirating the exposed cortex using a 32 gauge needle attached to a vacuum pump. The extent of the aspiration was guided using superficial landmarks (e.g., bottom of the skull and one millimeter anterior to the crista supratympanica). Hemorrhaging was controlled by application of ice-cold saline and gel foam. For controls ($n = 8$), the craniotomy was performed but the dura was left intact. The same procedures were performed on animals in the combined entorhinal/perirhinal cortex lesion group (EntPr, $n = 5$), but in addition, aspiration lesions extended 2 mm forward from the crista supratympanica and the medial entorhinal cortex was lesioned electrolytically (1 mA, anodal direct current, 7–10 sec) using monopolar stainless steel electrodes insulated with epoxy to within 200 μ m of the tip. Electrode placement was guided by coordinates modified from an atlas of the rat brain (Paxinos and Watson, 1986). The anterior-posterior (AP), medial-lateral (ML), and dorsal-ventral (DV) coordinates were computed in relation to the interaural line (AP = 2.0, ML = ± 4.0 , DV = 2.0). For EntPr controls, only the craniotomy was performed.

For animals in the fornix lesion group (FX, $n = 8$), the fornix and fimbria were lesioned electrolytically. Two lesions were placed in each

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hemisphere (AP = 7.6, ML = ± 0.5 , DV = 3.2 from dura; AP = 7.6, ML = ± 1.5 , DV = 3.2 from dura). For controls ($n = 6$) the electrode was lowered to the same locations but no current was passed. After surgery the wound was sutured and the animal was placed under a heat lamp until recovery from anesthesia was complete. Animals were then returned to the housing area and allowed to recover for 14 d before training began.

Conditioning apparatus and procedure for fear conditioning. Rats were placed individually into a rodent conditioning chamber (Coulbourn Instruments Inc., Lehigh Valley, PA, model E10-10) enclosed by a sound-attenuating cubicle (Coulbourn Instruments Inc., model E10-20). Stimulus presentation was controlled by a microprocessor and a digital I/O board (Opto 22). The CS was a 10 kHz tone produced by a frequency generator (Coulbourn Instruments Inc., model S81-06), amplified to 75 dB, and presented for 20 sec through a speaker located in the front panel of the chamber. The US was a brief (500 msec) distributed delivery of current (0.5 mA) produced by a grid floor shocker (Coulbourn Instruments Inc., model E13-08).

On day 0, animals were placed in the conditioning apparatus for 20 min with no stimuli presented. On days 1 and 2, Pavlovian conditioning trials were given during which two CS presentations each coterminated with the US (ITI = 60–120 sec). On day 3, control and lesioned groups received the CS on the same schedule as on the previous 2 d, but without US presentation.

Freezing was used as an index of conditioned fear (Blanchard and Blanchard, 1969; Bouton and Bolles, 1980; Fanselow, 1980; LeDoux et al., 1984) and was assessed by viewing the animals through a peephole in the sound-attenuating chamber. Freezing involved the absence of all movement, except for respiratory-related movements, while the animal was in the stereotyped crouching posture (Blanchard and Blanchard, 1969); standing motionless but without crouching was not scored as freezing. Fear conditioning to the phasic CS was measured during the first 20 sec CS presentation on each day. Contextual fear conditioning was assessed by measuring freezing during the 20 sec prior to the onset of the first CS of each day, as previously described (Phillips and LeDoux, 1992, 1994).

Apparatus and procedure for passive avoidance. Several days after extinction criterion was met in the fear conditioning procedure (less than 5 sec of freezing during a trial on 2 consecutive days of extinction trials), Ent animals were placed in a novel environment on a platform (7 cm $\times$ 10 cm $\times$ 2 cm) situated on a grid floor connected to a grid floor shocker (Coulbourn Instruments, model E13-08) in a clear plastic box. Latency to step off the platform was recorded. Two hours later, animals were again placed on the platform and were given a 1 mA, 500 msec footshock when two paws touched the grid floor. On the next day (testing), animals were placed on the platform and the latency to step down was recorded. The procedure was based on Izquierdo et al. (1993).

Histology. After completion of behavioral studies animals were given an overdose of sodium pentobarbital (120 mg/kg) and transcardially perfused with physiological saline, followed by 10% buffered formalin. Brains were postfixed in buffered formalin for 1 d to 2 weeks, frozen, and cut coronally on a sliding microtome or cryostat into 40 μ m sections. Every fourth section was mounted on a gelatin-coated slide, allowed to air dry, and stained with thionine.

Results

Entorhinal cortex lesions and fear conditioning

Histological analysis of animals with lesions aimed at the entorhinal cortex revealed that in most cases the vast majority of the entorhinal cortex as well as posterior portions of the perirhinal cortex, and in some cases ventral subiculum and CA1, were removed (see Fig. 1). Animals were excluded from the statistical analysis if there was less than 75% damage to the entorhinal cortex (extent of damage was estimated from serial reconstruction of coronal sections). Ent animals included in the analysis ($n = 8$) had between 75% to 100% of the entorhinal cortex removed (control $n = 8$).

The effects of entorhinal cortex lesions on the acquisition of freezing responses to contextual cues and to the primary CS were analyzed across days by performing an analysis of variance with one grouping variable [surgery (lesion or control)], and two repeated measures [stimulus type (context or CS) and day (1–

Figure 1. Serial frontal sections illustrating a typical lesion of the entorhinal cortex. Sections are from rostral to caudal (a–e), with stippling indicating the lesion site.

3]). The main effect of surgery was not significant [$F(1,13) = 0.28$, $p > 0.60$], nor was the interaction between surgery and type [$F(1,13) = 2.11$, $p > 0.16$] or surgery and day [$F(2,26) = 0.54$, $p > 0.58$] or surgery, type, and day [$F(2,26) = 0.78$, $p > 0.46$]. The main effect of day [$F(2,26) = 71.10$, $p < 0.001$] and

Figure 2. Effects of lesions of entorhinal cortex on the acquisition of conditioned freezing to the conditioned stimulus (CS; a tone) and to the background context. Error bars represent the SE below and above the mean (entorhinal, $n = 8$; control, $n = 8$).

of type [$F(1,13) = 17.34$, $p < 0.002$] were significant. In addition, there was a significant interaction of day and type [$F(2,26) = 14.58$, $p < 0.001$]. Thus, there was a difference in acquisition rate between context and CS conditioning in controls, as previously reported (Phillips and LeDoux, 1992), and damage to entorhinal cortex did not affect this (see Fig. 2).

Ent lesions and passive avoidance

The failure of our Ent lesions to affect hippocampal dependent contextual conditioning led us to examine whether our Ent lesions would affect performance on a step-down passive avoidance task which has been shown to be sensitive to disruption of entorhinal cortex (Izquierdo et al., 1994) and hippocampal function (see O'Keefe and Nadel, 1978; Gray, 1982). The latency to step down from the platform on day 1 (training) was measured in comparison to the latency on day 2 (testing) (Table 1). The effects of entorhinal cortex lesions on this task were analyzed by performing an analysis of variance with one grouping variable [lesion (control or lesion)] and one repeated measure [day (training or testing)]. The main effect of day was significant [$F(1,14) = 15.47$, $p < 0.005$], as well as the interaction between

Table 1. Group averages of step-down latency

Group	<i>N</i>	Training latency	Test latency
Sham lesion	5	6.6 (± 3.1) sec	93.6 (± 21.4) sec*
Ent lesion	9	17.7 (± 8.7) sec	37.0 (± 19.7) sec

Data presented are $\pm$ SE, measured in seconds. See Results for further explanation.

* $p < 0.001$ compared to controls.

day and lesion [$F(1,14) = 6.25$, $p < 0.05$]. Post hoc t tests revealed a significant difference between training and testing for control animals [$t(14) = 7.70$, $p < 0.01$], but not for Ent animals [$t(14) = 1.72$, $p > 0.05$] (see Table 1). Little or no freezing, defined as motionless "crouching," was exhibited by either the control or lesion animals when placed on the platform in the conditioning chamber during training or testing.

EntPr lesions and fear conditioning

Perirhinal cortex receives inputs from a wide range of cortical areas (Deacon et al., 1983; Romanski and LeDoux, 1994) and projects directly to the hippocampal formation (Kosel et al., 1983). To test the possibility that perirhinal cortex might be an alternative route between cortical areas and the hippocampus that might mediate contextual fear conditioning, we examined the effects of combined lesions of the entorhinal and perirhinal cortex (EntPr). The lesions included much of the medial and lateral entorhinal cortex and the perirhinal cortex as far anterior as the amygdala. Animals were included if more than 75% of the entorhinal and perirhinal cortex was ablated, with lesion size evaluated from serial reconstructions ($n = 5$; controls, $n = 8$). A typical lesion is reconstructed in Figure 3. Some lesions included ventral CA1 and subiculum, as well as the entorhinal and perirhinal areas.

The effects of EntPr lesions were analyzed using the same design as described above for Ent animals and fear conditioning (ANOVA with one grouping variable and two repeated measures). There was a main effect of day [$F(2,16) = 84.0$, $p < 0.001$], but not surgery, nor an interaction between the two. A main effect of type was significant [$F(1,8) = 7.72$, $p < 0.025$], as well as an interaction of day and type [$F(2,16) = 8.51$, $p < 0.025$]. No other main effect or interaction was significant (see Fig. 4). There was a difference in the acquisition rate for animals depending on stimulus type, and damage to the rhinal cortex did not affect this.

Fornix lesions and fear conditioning

The failure of Ent or combined EntPr lesions to affect contextual fear conditioning led us to examine the effects of lesions of the fornix, which provides another major source of hippocampal input and output connections (Swanson and Cowan, 1977; Amaral, 1987). Lesions of the fornix (FX) typically included the fornix as well as the fimbria and in some cases the anterior pole of the hippocampus or part of the medial septum ($n = 8$; see Fig. 5; control $n = 6$).

The effects of fornix lesions were analyzed using the same design as above. The main effect of day [$F(2,26) = 77.26$, $p < 0.001$] and type [$F(1,13) = 10.14$, $p < 0.01$] and the interaction between day and type [$F(2,26) = 5.92$, $p < 0.01$] were significant. Although the main effect of surgery was not significant, nor the interaction between surgery and day, the interaction of surgery and type was significant [$F(1,13) = 4.74$, $p < 0.05$]. In

Figure 3. Serial frontal sections illustrating a typical combined lesion of the entorhinal and perirhinal cortex. Sections are from rostral to caudal (a-e), with stippling indicating the lesion site.

addition, the three-way interaction of day, type, and surgery was significant [$F(2,26) = 3.40, p < 0.05$], indicating that there was a significant difference between FX animals and their controls, dependent upon the day and on the type of stimulus information

Figure 4. Effects of lesions of the combined lesion of the entorhinal and perirhinal cortex (EntPr) on the acquisition of conditioned freezing to the conditioned stimulus (CS; a tone) and to the background context. Error bars represent SE above and below the mean (EntPr, $n = 5$; control, $n = 8$).

to which the animals were responding (see Fig. 6). Evaluation of the data with post hoc t tests revealed that fornix lesions affect contextual conditioning on day 2 [$t(26) = 3.08, p < 0.002$] and day 3 [$t(26) = 4.43, p < 0.002$].

Discussion

Recent studies have implicated the hippocampal formation in contextual fear conditioning (Selden et al., 1991; Kim and Fanselow, 1992; Phillips and LeDoux, 1992, 1994). In the present study, we attempted to determine how information from the environment might reach the hippocampus in the process of forming contextual representations during fear conditioning. We began by making lesions in the entorhinal cortex, which is believed to be an important link between neocortical sensory processing systems and the hippocampus (van Hoesen, 1982; Amaral, 1987; Amaral and Witter, 1989). As these lesions did not interfere with conditioning to either the context or an explicit CS, combined lesions of the entorhinal and perirhinal cortex were made. The perirhinal cortex is known to have a direct connection with the hippocampal formation (Kosel et al., 1983) and the entorhinal cortex may have been bypassed. Perirhinal cortex also has con-

Figure 5. Serial frontal sections illustrating a typical lesion of the fornix (Fx). Sections are from rostral to caudal (a–e), with stippling indicating the lesion site.

nections with the amygdala (Burwell and Amaral, 1993; Romanski and LeDoux, 1993), which is also required for contextual conditioning (Phillips and LeDoux, 1992). The combined EntPr lesions had no effect. Another major source of input and output connections of the hippocampus is the fornix (Swanson and Cowan, 1977; Amaral, 1987). In contrast to the Ent and EntPr lesions, fornix lesions interfered with conditioning to context but

Figure 6. Effects of lesions of the fornix (Fx) on the acquisition of conditioned freezing to the conditioned stimulus (CS; a tone) and to the background context. Error bars represent SE above and below the mean; *, $p < 0.01$ (Fx, $n = 8$; control, $n = 6$).

not to an explicit CS. Since the fornix fibers link the hippocampus with subcortical structures, these results suggest that the conditioning of fear reactions to background or contextual stimuli may depend more on the transmission of information between subcortical areas and the hippocampus.

Rhinal cortex lesions (including lesions of the entorhinal, perirhinal, or parahippocampal regions) disrupt performance of a variety of hippocampal-dependent tasks (Olton et al., 1978; Staubli et al., 1986; Murray et al., 1989; Zola-Morgan et al., 1989; Meunier et al., 1990; Otto et al., 1991; Bunsey and Eichenbaum, 1993; Mumby and Pinel, 1994; Nagahara et al., 1995). Furthermore, recent studies suggest that lesions of this area are more effective than, or at least as effective as lesions of the hippocampus in producing amnesic effects on delayed-nonmatch-to-sample, or delayed-match-to-sample tasks, in both rats and monkeys (Zola-Morgan and Squire, 1985; Gaffan and Murray, 1992; Mumby and Pinel, 1994). Excitotoxic lesions of entorhinal cortex impair retention on tasks learned 2–3 weeks prior to surgery, but leave animals relatively unimpaired on tasks learned 4–6 weeks prior to surgery (Cho et al., 1993). Also, infusion of CNQX, AP5, or muscimol into the entorhinal cortex impairs performance on passive avoidance tasks (Ferreira et al.,

Figure 7. Schematic of the circuit for neocortical and subcortical hippocampal input and output.

1992; Izquierdo et al., 1993), which also depend upon the hippocampus (O'Keefe and Nadel, 1978; Gray, 1982). In spite of the fact that entorhinal cortex lesions typically replicate the effects of hippocampal lesions, entorhinal cortex lesions failed to affect contextual fear conditioning in the present study. A similar result (no effect of Ent lesions) has been recently reported in abstract form for two other hippocampal-dependent tasks (Jarrod and Hyko, 1994; Otto and Schiller, 1994).

Fornix lesions, which are often treated as analogous to lesions of the hippocampus (e.g., Gaffan, 1974; Eichenbaum et al., 1986), interfere with performance on spatial as well as nonspatial tasks (e.g., Eichenbaum et al., 1988; Raffaele and Olton, 1988). The present results are consistent with the relevant literature using lesions of the fornix as a method for evaluating the role of the hippocampal memory system, as fornix lesions disrupted contextual fear conditioning. Thus, subcortical inputs and outputs of the hippocampus (or cortical inputs that bypass the entorhinal and perirhinal cortex) may be sufficient in providing information to the hippocampus for conditioning to context and in controlling the transmission of information to others areas, such as the amygdala, which are required for the acquisition of the aversive association and the control of conditioned responses (Davis, 1992; Kapp, 1990; LeDoux, 1992, 1995). These findings raise questions concerning the exact inputs to the hippocampus necessary for conditioning to context (see Fig. 7).

Although entorhinal cortex lesions did not disrupt contextual fear conditioning, they affected passive avoidance conditioning. This is of interest given that passive avoidance is often considered a form of contextual fear conditioning, and like contextual fear conditioning is dependent on the hippocampus (O'Keefe and Nadel, 1978; Gray, 1982; Selden et al., 1991). However, passive avoidance is most similar to the form of contextual conditioning that involves the delivery of the US without a CS. We have termed this "foreground contextual conditioning," to distinguish it from the situation in which an explicit CS, such as a tone, is paired with a US, and the contextual stimuli are in the background against this primary association (Phillips and LeDoux, 1994). Given that we found that hippocampal lesions affected background but not foreground contextual conditioning (Phillips and LeDoux, 1994), it is surprising that entorhinal cortex lesions have an effect on passive avoidance conditioning (a

foreground contextual task) but have no effect on background contextual conditioning. But the role of the hippocampus in passive avoidance and background contextual fear conditioning may be different. That this is the case is suggested by the fact that neither the Ent or control animals exhibited much freezing behavior in the passive avoidance chamber. Although contextual conditioning and passive avoidance learning are superficially similar, they may be very different processes. It may be that the entorhinal cortex is required, not as an input to the hippocampus in passive avoidance conditioning, but as an output required to control instrumental behavior. Except for the presence of the "safe" platform in the passive avoidance task, the chambers were similar in the two tasks. However, the presence of the safe area makes the shock avoidable and drastically alters the behavioral opportunities available to the animal. While classically conditioned freezing is an involuntarily elicited respondent controlled by antecedents (Bouton and Bolles, 1980), the passive avoidance response is a voluntary instrumental response, an operant controlled by its consequences. As a result, passive avoidance may require cortical systems and their interactions with basal ganglia motor systems (Mink and Thach, 1993). Thus, lesions of the entorhinal cortex might have been effective at disrupting acquisition of the passive avoidance task because contextual information from the hippocampus cannot reach these motor circuits rather than because sensory information cannot reach the hippocampus. Resolution of the difference between the effects of contextual fear conditioning and passive avoidance conditioning might suggest some important insights into the anatomical systems that allow the hippocampus to control fundamentally different kinds of behaviors, perhaps as fundamentally different as voluntary versus involuntary emotional responses, in reaction to the same stimulus information.

Although it is widely believed that the entorhinal cortex is a critical relay for sensory inputs to the hippocampus, recent studies have suggested that some sensory (visual) information reaches the hippocampus directly from the thalamus (Mizumori et al., 1993) and visual association cortex (Shi et al., 1994). Whether these pathways or other more indirect routes might be involved is not known. Also, it is unclear whether the entorhinal cortex might normally be the preferred pathway and the subcortical routes are only used when the preferred pathway is damaged.

What is clear, though, is that in the absence of the entorhinal cortex, contextual conditioning can proceed at a normal rate. Further study is required to determine the exact afferent pathways to the hippocampus that are necessary for background or contextual fear conditioning.

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