

## Brief Communication

## Delayed Recall of Fear Extinction in Rats With Lesions of Ventral Medial Prefrontal Cortex

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Extinction of auditory fear conditioning is thought to form a new memory. We previously found that rats with vmPFC lesions could extinguish fear to the tone within a session, but showed no recall of extinction 24 h later. One interpretation is that the vmPFC is the sole storage site of extinction memory. However, it is also possible that lesioned rats were unable to retrieve extinction memory stored in other structures. To determine if a latent extinction memory could be retrieved with additional training, we repeated the experiment but added an additional 5 d of extinction reminder trials. Replicating our previous findings, vmPFC-lesioned rats extinguished normally on day 1, but showed no recall of extinction on day 2. Over the next 5 d, however, lesioned rats showed significant savings in their rate of re-extinction. Thus, the vmPFC is not the only site where extinction memory is stored. Nevertheless, lesioned rats receiving only two extinction trials per day required twice as many days to initiate extinction as controls. Although recall of extinction is possible without the vmPFC, it is significantly delayed. We suggest that the vmPFC accelerates extinction by permitting access to recently learned extinction trials, thereby maximizing behavioral flexibility.

Behavioral experiments dating back to Pavlov (1927) indicate that extinction training does not erase memory for conditioning, but forms a new memory (Pavlov 1927; Konorski 1967). In auditory fear conditioning, freezing to a tone-conditioned stimulus rapidly extinguishes when tones are given without a footshock, and remains low for several days thereafter. With sufficient time, however, freezing responses spontaneously recover to their original levels (Quirk 2002). Thus, extinction induces a long-term memory that competes with memory of conditioning for control of behavior (Bouton 1993; Rescorla 2001).

The neural circuits that learn and store extinction memory are just beginning to be explored (see Myers and Davis 2002). Retention of fear extinction involves the ventral medial prefrontal cortex (vmPFC; Morgan et al. 1993, 2003; Morrow et al. 1999; Quirk et al. 2000; but see Gewirtz et al. 1997). We previously observed that rats with vmPFC lesions extinguished normally within a session, but were unable to recall extinction the following day, exhibiting the same levels of freezing as a no-extinction control group (Quirk et al. 2000). Consistent with this, infralimbic vmPFC neurons show increased tone responses 24 h after extinction training, when rats are recalling extinction (Milad and Quirk 2002). Similar potentiation of mPFC during extinction recall has been observed with evoked potentials (Herry and Garcia 2002) and metabolic activity (Barrett et al. 2003).

The fact that vmPFC-lesioned rats can learn extinction but cannot recall it the following day is consistent with the hypothesis that vmPFC is a critical site of extinction consolidation and storage (Quirk et al. 2000; Garcia 2002). However, it is also possible that the vmPFC is necessary for retrieval of extinction stored in other structures. One way to distinguish between these possibilities would be to look for savings in the rate of re-extinction across days (Rescorla 2002). A latent extinction memory would be expected to accelerate the rate of relearning. Because our previous study assessed recall of extinction at a single time point

only (24 h after training), it was not possible to determine if lesioned rats could eventually recall extinction, if given additional days of training. To address this, we repeated our experiment in which vmPFC-lesioned rats were conditioned and extinguished in a single day. Rats then received spaced extinction training (two trials per day) on days 2–7, to determine if there was any savings in the rate of re-extinction. We also examined the effects of vmPFC lesions in rats that received only spaced extinction training. Our general aim was to determine the longevity of vmPFC-lesion effects in this paradigm.

## RESULTS

## Histology

Electrolytic lesions targeted the infralimbic (IL) and ventral prefrontal (PL) subdivisions of mPFC. Figure 1A shows a photomicrograph of a typical lesion. A schematic diagram indicating the extent of the lesions in all animals is shown in Figure 1B. As in our previous study (Quirk et al. 2000), rats with <70% bilateral damage to IL were excluded. Rats were also excluded if they had significant damage to the dorsal mPFC or white matter. Rats that were included had significant damage in IL, ventral PL, as well as minor damage to the medial and ventral orbital cortex and the rostral septum. A total of 16 vmPFC-lesioned and 22 sham-operated rats were studied.

## vmPFC Lesions Impaired 24-h Recall of Extinction

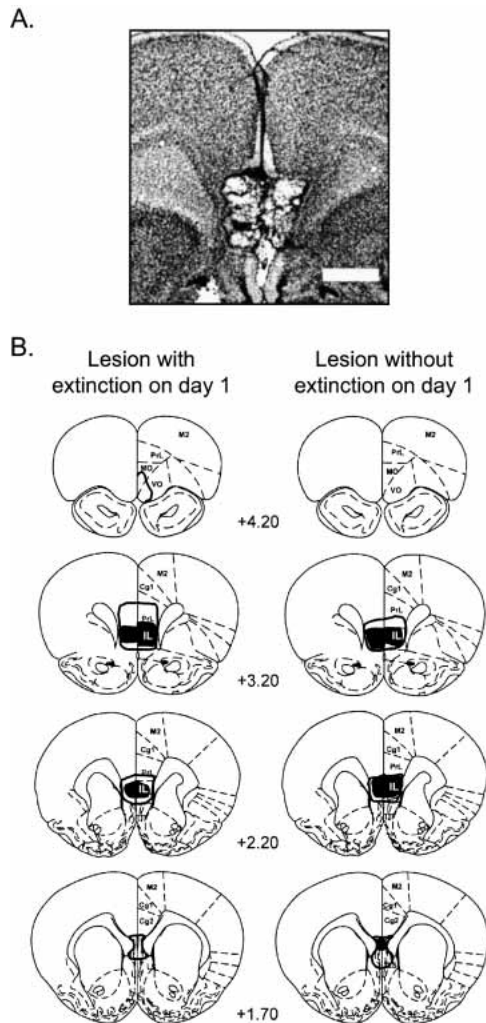
Sham-operated rats that received extinction training on day 1 (sham-ext,  $n = 11$ ) were compared with lesioned rats that were also given extinction training on day 1 (lesion-ext,  $n = 11$ ) and to sham-operated rats and lesioned rats that did not receive extinction on day 1 (sham-no-ext,  $n = 11$ , and lesion-no-ext,  $n = 5$ , respectively). All four groups acquired similar levels of conditioned freezing and suppression of bar-pressing for food (Fig. 2). Freezing values in the last two trials of conditioning were 52.3%, 60.9%, 60.4%, and 62.3% for sham-ext, lesion-ext, sham-no-ext, and lesion-no-ext, respectively. Suppression ratios were 1.0, 0.9, 0.9, and 1.0, respectively. One-way ANOVA showed no significant difference between groups in either measure (freezing:  $F_{(3,34)} = 1.1$ ,  $P > 0.05$ ; suppression:  $F_{(3,34)} = 0.9$ ,  $P > 0.05$ ). One

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**Figure 1** Electrolytic lesions of the ventromedial prefrontal cortex (vmPFC). (A) Photomicrograph illustrating a typical lesion of vmPFC damaging the entire infralimbic area and the ventral half of the prelimbic area (calibration bar, 1 mm). (B) A schematic diagram showing the extent of the lesions for two experimental groups: lesion with extinction on day 1, and lesion without extinction on day 1. Filled and outline areas represent smallest and largest lesions, respectively. (IL) Infralimbic nucleus; (PrL) prelimbic cortex; (Cg1) anterior cingulate cortex; (DP) dorsal peduncular nucleus; (LS) lateral septum; (MO) medial orbital cortex; (M2) secondary motor cortex; (VO) ventral orbital cortex. Numbers indicate anterior coordinate relative to bregma (from Paxinos and Watson 1998).

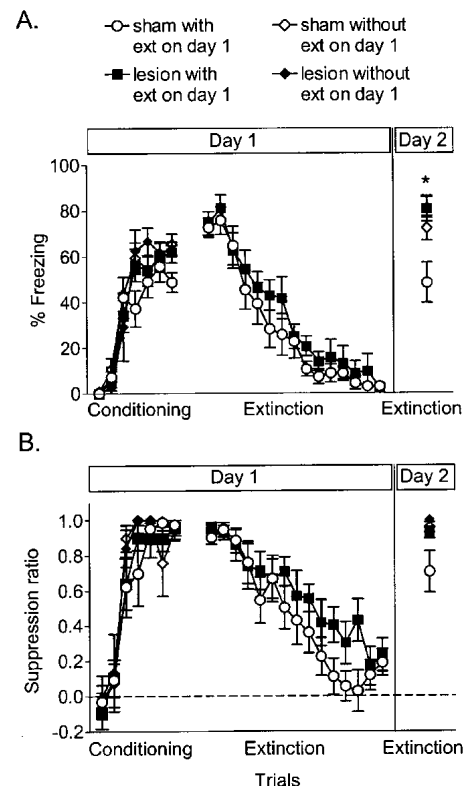
hour after conditioning, sham-ext and lesion-ext groups extinguished at similar rates, reaching negligible levels of freezing by the end of the session (sham-ext: 3.0%; lesion-ext rats: 2.4%). Suppression was similarly extinguished in both sham-ext rats and lesion-ext rats, reaching 0.2 by the end of the session. ANOVA of suppression values showed no significant difference between groups during extinction ( $F_{(1,20)} = 1.7, P > 0.05$ ).

On day 2, however, lesion-ext rats showed much higher freezing than sham-ext rats, indicating poor recall of extinction. Lesion-ext rats froze 81% at the start of day 2, compared with only 48% in the sham-ext group. In fact, freezing in the lesion-ext rats was not significantly different from the no-extinction groups (sham-no-ext: 72%; lesion-no-ext: 81%). One-way ANOVA on day 2 indicated a significant effect of group ( $F_{(3,34)} = 5.2, P < 0.01$ ), with post hoc comparisons showing that lesion-ext rats froze significantly more than sham-ext rats

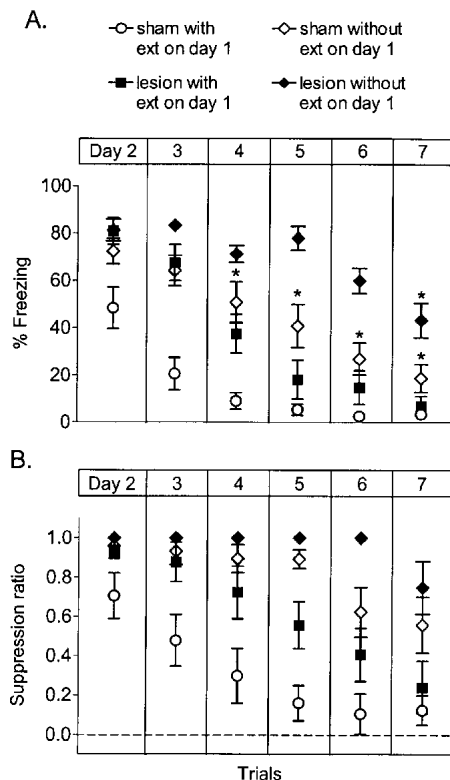
( $P < 0.01$ ). The suppression measure also showed increased fear in lesion-ext rats compared with the sham-ext group (0.93 vs. 0.70), but post hoc comparisons did not show significant between-group differences, most likely because of a ceiling effect. Thus, as we previously reported (Quirk et al. 2000), rats with vmPFC lesions were able to extinguish conditioned fear responses on day 1, but were unable to recall extinction 24 h later.

### vmPFC-Lesioned Rats Could Eventually Recall Massed Extinction Training, But Were Delayed in Spaced Extinction Training

All four groups were given spaced extinction training for an additional 5 d (two trials per day), and were compared in their rate of across-day extinction (Fig. 3). Lesioned rats that received extinction on day 1 (lesion-ext) extinguished considerably faster on days 2–7 than lesioned rats that did not receive extinction on day 1 (lesion-no-ext), demonstrating that lesion-ext rats could eventually recall the massed extinction training session. Therefore, extinction memory was not totally lost in lesioned animals. A two-way ANOVA revealed a main effect of group ( $F_{(3,34)} = 14.7, P < 0.001$ ), trial block ( $F_{(5,170)} = 70.6, P < 0.001$ ), and interaction ( $F_{(15,170)} = 4.9, P < 0.001$ ). Post hoc comparisons indicated that freezing in lesion-ext rats was significantly lower than lesion-no-ext rats on days 4, 5, 6, and 7 (all  $P$ s  $< 0.01$ ), confirming savings in the rate of re-extinction in lesion-ext rats.



**Figure 2** vmPFC-lesioned rats could learn extinction but could not recall extinction the following day. (A) Percent freezing to the tone. (B) Suppression of bar-pressing for food. Single trials are shown throughout. Four groups were studied: sham-operated rats with (or without) extinction training on day 1, and vmPFC-lesioned rats with (or without) extinction training on day 1. There were no significant differences between groups during conditioning or extinction on day 1. On day 2, however, sham-operated rats that received extinction on day 1 were lower than the other groups ( $P < 0.05$ , ANOVA main effect), indicating recall of extinction learning. Lesioned rats were not able to recall extinction on day 2.



**Figure 3** vmPFC-lesioned rats could eventually recall massed extinction training, but were delayed in spaced extinction training. (A) Percent freezing and (B) suppression of bar-pressing for food to the first tone of the day (two tones were given per day). Lesioned rats with prior extinction experience extinguished significantly faster than lesioned rats without prior extinction experience (see text for statistics). This demonstrates that despite high levels of spontaneous recovery, lesioned rats could eventually recall extinction from day 1. Nevertheless, lesioned rats without massed extinction training on day 1 extinguished significantly more slowly than similarly treated sham-operated rats. Asterisks indicate significant decline in freezing, compared with day 2 (within-groups,  $P < 0.05$ , post hoc test). Note that lesioned rats required 6 d of extinction training to show a significant decrease in freezing, compared with only 3 d in sham-operated rats.

Importantly, lesion-no-ext rats extinguished considerably slower than sham-no-ext rats, indicating that vmPFC lesions impair across-day extinction. Within-group comparisons indicated that lesion-no-ext rats did not show significant extinction until day 7, compared with day 4 in sham-no-ext rats (all  $P$ s  $< 0.05$ ). Thus, lesioned rats required twice the amount of extinction training (6 d vs. 3 d) to initiate extinction. Analysis of suppression showed a similar trend (see Fig. 3B); with a significant effect of group ( $F_{(3,34)} = 10.7$ ,  $P < 0.001$ ) and phase ( $F_{(5,170)} = 15.6$ ,  $P < 0.001$ ), but not interaction ( $F_{(15,170)} = 1.4$ ,  $P > 0.05$ ).

## DISCUSSION

We have replicated our previous findings (Quirk et al. 2000) that rats with lesions of vmPFC were able to learn extinction within a session, but were unable to recall extinction 24 h later. We now extend these findings by showing that vmPFC-lesioned rats could eventually recall their original extinction training if given additional training over days. With only spaced extinction training, lesioned rats required twice as many days as controls to show a significant reduction in freezing. Thus, vmPFC-lesioned rats could eventually learn extinction, but they were significantly delayed.

Despite high recovery of freezing on day 2, savings in the rate of re-extinction indicate that lesioned rats were not fully amnesic for their original extinction training. This is similar to the within-session savings we observed in our prior lesion study (Quirk et al. 2000). Thus, other structures are capable of storing and expressing extinction. Considerable evidence suggests that the amygdala contributes to extinction storage. For example, intra-amygdala infusion of the NMDA-receptor antagonists (Falls et al. 1992; Lee and Kim 1998; Lin et al. 2003), kinase inhibitors (Lu et al. 2001; Lin et al. 2003), and anisomycin (Lin et al. 2003) blocks extinction of conditioned fear. Extinction might also be stored in other parts of the prefrontal cortex not lesioned in our study. In addition to the infralimbic area, more dorsal and lateral parts of mPFC have been shown to increase their metabolic activity when rats are recalling extinction (Barrett et al. 2003), consistent with a role in extinction memory.

Despite storage of extinction outside the vmPFC, rats without the vmPFC had difficulty accessing extinction learned the previous day. Furthermore, in a spaced protocol, lesioned rats required twice as many days as controls to initiate extinction, similar to an earlier observation (Morgan et al. 1993). This suggests that vmPFC facilitates extinction, either by retrieving extinction stored in other structures (Ranganath et al. 2000; Sakai 2003; Phillips et al. 2004) or by storing some portion of extinction memory, or both. Using a similar protocol as the present study, infralimbic neurons showed robust potentiation of tone-evoked responses 24 h after extinction training, when rats were recalling extinction (Milad and Quirk 2002). A similar result was obtained with evoked potentials in mPFC (Herry and Garcia 2002). In both cases, the degree of mPFC potentiation was correlated with recall of extinction. These findings are consistent with both consolidation and retrieval roles of mPFC in extinction. We recently observed, however, that infusion of the protein synthesis inhibitor anisomycin into the mPFC just prior to extinction training blocked long-term, but not short-term, memory for fear extinction (Santini et al. 2004). Furthermore, there was no savings in the rate of re-extinction in anisomycin-infused animals, consistent with a storage deficit. Thus, mPFC does appear to be involved in consolidation of extinction. Interestingly, infusing anisomycin into the vmPFC appears to have a greater effect than lesioning vmPFC, because savings were observed with the latter but not the former. Perhaps this difference is due to some degree of recovery of function in lesioned rats, compared with anisomycin-infused rats.

In summary, we have shown that vmPFC accelerates fear extinction by facilitating recall of extinction across days. The vmPFC appears to be particularly important during the initial days of extinction training. It was recently shown that spaced extinction trials can act as reminders of conditioning, causing incubation of fear that opposes extinction (Cain et al. 2003). Extinction-induced activation of infralimbic mPFC neurons, and resulting inhibition of the amygdala (Quirk et al. 2003; Rosenkranz et al. 2003; Milad et al. 2004), may be necessary to overcome incubation and initiate extinction. Rapid initiation of extinction is necessary for reversal learning, which is consistent with mPFC lesion deficits in tasks requiring behavioral flexibility (Delatour and Gisquet-Verrier 2000; Ragozzino et al. 2003; Schoenbaum et al. 2003).

## MATERIALS AND METHODS

### Subjects

The methods were similar to those used in our previous study (Quirk et al. 2000). The procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of the Ponce



School of Medicine in compliance with the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals (NIH Publication No. 80-23). Male Sprague-Dawley rats weighing ~300 g were housed individually in transparent polyethylene cages and maintained on a 12-h light/dark schedule with free access to water. Rats were food-deprived (15 g/d of rat chow) to reduce their body weight to 85%. During this period (1 wk), rats were handled daily and acclimated to 45-mg food pellets (Bioserve Inc.). After food deprivation, rats were transferred to the laboratory, where they were located in a negative-pressure clean room (Colorado Clean Room). Rats were trained to press a bar for food. Bar-pressing was used to maintain a constant activity level against which freezing could be more reliably measured (Quirk et al. 2000; Santini et al. 2001). A continuous reinforcement schedule was gradually reduced to a variable interval schedule with reinforcement available every 60 sec (VI-60). Rats learned to press at a rate  $\geq 20$ /min.

### Surgery

Atropine sulfate (0.24 mg/kg, i.p.) was injected 15 min prior to ketamine (74 mg/kg)–xylazine (11 mg/kg) solution. Rats were placed into a stereotaxic apparatus (David Kopf Instruments), and an incision was made in the skin to expose the skull. Two burr holes (one on each hemisphere) were drilled bilaterally with a dental drill. A Teflon-insulated electrode (125  $\mu$ m, 0.5 mm tip; Rhodes Medical Instruments) connected to a DC stimulator with constant current output (Grass Astro Med) was lowered into vmPFC, targeting the infralimbic cortex (IL). The coordinates related to bregma were as follows: 2.9 mm anterior, 0.5 mm lateral, and 4.9 mm ventral (Paxinos and Watson 1998). The electrolytic lesion was made by passing 1.0-mA anodal current through the electrode for 14 sec. In sham-operated rats, the same coordinates were used except that the electrode was lowered to 2.4 mm and no current was passed. After removing the electrode, the burr holes were filled with bone wax, the skin was sutured, and a topical antibiotic was applied to prevent infection. Rats were injected with buprenorphine hydrochloride (Buprenex, 0.02 mg/kg, i.m.) and allowed 1 wk to recover.

### Fear Conditioning

All rats received fear conditioning and extinction in an operant chamber while pressing for food. The chamber (Coulbourn Instruments) was 25  $\times$  29  $\times$  28 cm with aluminum and Plexiglas walls and a grid floor with 0.5-cm steel bars spaced at 1.8 cm. A response bar was positioned 6.5 cm above the floor, and a speaker was mounted on the outside wall opposite to the bar; illumination was provided by single overhead light. The chamber was situated inside a sound-attenuating box (Med Associates) to reduce ambient sound to 55 dB. The conditioned stimulus (CS) was a 4-kHz tone lasting for 30 sec, with a loudness of 80 dB SPL. The unconditioned stimulus (US) was a scrambled footshock delivered to the rats through the grid floor with an intensity of 0.5 mA and a duration of 0.5 sec. The footshock coterminated with the tone. The average intertrial interval (ITI) was 4 min (range, 2–6 min). Rats were conditioned four at the same time in separate chambers. All phases of training were given in the same chamber.

There were four experimental groups: sham-operated rats and vmPFC-lesioned rats with extinction training on day 1 (sham-ext and lesion-ext, respectively), and sham-operated rats and vmPFC-lesioned rats with no extinction training on day 1 (sham-no-ext and lesion-no-ext, respectively). The experiment took place over 7 d. On day 1, rats in all groups received five trials of tone alone (habituation phase) followed immediately by seven trials of tone paired with footshock (conditioning phase). Then, 1 h after conditioning, rats in the sham-ext and lesion-ext groups received 15 trials of tone alone (massed extinction phase), whereas sham-no-ext and lesion-no-ext rats remained in their home cages. From days 2 to 7, all rats were given two extinction tones per day (spaced extinction phase).

### Histology

After the experiment, all rats received an overdose of pentobarbital (100 mg/kg, i.p.) and were transcardially perfused with 0.9%

saline solution followed by 10% buffered formalin. Brains were removed and stored in 30% sucrose/formalin solution. Coronal sections (40  $\mu$ m thick) were cut with a freezing microtome, mounted onto gelatin-coated slides, and stained with thionin. For display purposes, lesions were traced onto drawings taken from a stereotaxic atlas (Paxinos and Watson 1998). Decisions to include or exclude animals were based on anatomical criteria, applied blind with respect to behavioral results.

### Data Analysis

Percent of time spent freezing and suppression of bar-pressing for food were used to measure conditioned fear during the experiment. Freezing is the absence of all movements except those related to respiration (Blanchard and Blanchard 1972). The total time spent freezing during the 30-sec tone was scored with a digital stopwatch from videotapes. Observers scoring freezing were blind with respect to the experimental groups. For the suppression measure, bar presses were time-stamped, stored on disk, and analyzed in Excel. The rates of bar-pressing 60 sec prior to the tone (pretone) were compared with the rates during the 30-sec tone as follows: suppression ratio = (pretone – tone)/(pretone + tone) (Quirk et al. 2000; Santini et al. 2001). A value of 1 indicated complete suppression of bar-pressing during the tone, whereas a value of 0 indicated no suppression. Freezing and suppression values were analyzed using ANOVA with repeated measures (Statistica, Statsoft). Post hoc comparisons were performed with the Tukey HSD method.

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