



Chronic stress impairs recall of extinction of conditioned fear

Angela D. Miracle, Michael F. Brace, Kellie D. Huyck, Samantha A. Singler,
Cara L. Wellman *

Department of Psychological and Brain Sciences and Program in Neuroscience, Indiana University, Bloomington, IN 47405, USA

Received 23 August 2005; revised 20 October 2005; accepted 23 October 2005

Abstract

Chronic restraint stress produces retraction of apical dendrites of pyramidal neurons in medial prefrontal cortex. To begin to examine the functional significance of this dendritic reorganization, we assessed the effects of chronic restraint stress on a prefrontally mediated behavior, extinction of conditioned fear. After bar press training to obtain a baseline of activity against which to measure freezing, rats were either unstressed or stressed via placement in a plastic restrainer (3 h/day for 1 week). After an additional day of bar press training, rats underwent fear conditioning and extinction. Rats received five habituation trials to a 30-s tone (4.5 kHz, 80 db) followed by seven pairings of tone and footshock (500 ms, 0.5 mA). One hour later, rats received tone-alone extinction trials to criterion. The next day, rats received 15 additional extinction trials. Percent freezing was assessed during all phases of training. Stress did not significantly affect unconditioned responding to tone, acquisition of conditioned fear, or initial extinction, but significantly increased freezing on extinction day 2. Thus, consistent with the regressive dendritic changes seen in medial prefrontal cortex, one week of restraint stress specifically impaired recall of extinction, a pattern of deficits typical of animals with impaired medial prefrontal function.

© 2005 Elsevier Inc. All rights reserved.

Keywords: Medial prefrontal cortex; Fear conditioning; Extinction; Rat

1. Introduction

Medial prefrontal cortex (mPFC) is a target for glucocorticoids involved in the stress response (Meaney & Aitken, 1985), and exposure to stressors results in a variety of neurochemical changes in mPFC, including increases in glutamate and acetylcholine release (Bagley & Moghaddam, 1997; Jedema & Moghaddam, 1994; Mark, Rada, & Shors, 1996; Moghaddam, 1993). Dendritic morphology of mPFC appears to be particularly sensitive to chronic stress: either six (Radley et al., 2004) or three hours (Cook & Wellman, 2004) of restraint per day for three weeks results in retraction of apical dendrites of layer II–III pyramidal neurons in mPFC. This effect occurs with as little as one week of brief daily restraint (Brown, Henning, & Wellman, 2005),

suggesting that the morphology of mPFC is exquisitely sensitive to stress.

Given that the geometry of the dendritic arbor (e.g., dendritic branching patterns, distribution, and overall shape) determines many functional properties of neurons (e.g., Grudt & Perl, 2002; Koch & Segev, 2000; Lu, Inokuchi, McLachlan, Li, & Higashi, 2001; Mainen & Sejnowski, 1996; Rall et al., 1992), the pronounced stress-induced dendritic changes in mPFC likely result in important functional changes that may have consequences for the behaviors mediated by mPFC. To begin to examine the functional significance of chronic stress effects in mPFC, we assessed the effects of chronic restraint stress on a prefrontally mediated behavior, extinction of conditioned fear. Lesions of mPFC impair extinction learning (Morgan & LeDoux, 1995; Quirk, Russo, Barron, & Lebron, 2000); in addition, electrophysiological data have demonstrated that firing of neurons in ventral mPFC is correlated with memory for fear extinction (Milad & Quirk, 2002), and consolidation of extinction is

* Corresponding author. Fax: +1 812 855 4691.

E-mail address: wellmanc@indiana.edu (C.L. Wellman).

impaired by blockade of protein synthesis in ventral mPFC (Santini, Ge, Ren, de Ortiz, & Quirk, 2004).

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (175–200 g, 48–50 days old at initiation of experiment; Harlan, Indianapolis, IN), were individually housed in a vivarium with a 12:12 h light/dark cycle (lights on at 7 AM) and ambient temperature of 23–25 °C. To motivate rats for bar pressing, weights were gradually reduced to 85% of free-feeding weight; rats were then maintained at this weight with weekly increases allowed for normally occurring weight gain. All experimental procedures occurred between 9:30 AM and 5:00 PM. All experimental procedures were approved by the Bloomington Institutional Animal Care and Use Committee and were conducted in accordance with USPHS and NIH guidelines.

2.2. Bar press training

To obtain a baseline level of activity against which to measure freezing, rats were trained to bar press for food reinforcement (see Quirk et al., 2000). Each rat was placed in an operant chamber within a sound-attenuating cabinet (Med Associates, St. Albans, VT). The chamber contained one operant lever on either side of a food receptacle, a house light on the opposite wall, a cue light over each lever, and a floor consisting of metal rods. The house light and the cue light over the reinforced lever were illuminated throughout each session. Rats were shaped to press the left lever for a food pellet reinforcer (BioServ pellets, Holton Industries, Frenchtown, NJ); shaping lasted 1–2 sessions, after which the reinforcement schedule was gradually reduced over several days from FR-1 to VI-60. Computer-based operant software (MedPCIV; Med Associates, St. Albans, VT) controlled pellet delivery.

2.3. Restraint stress

Following the final bar press training session, rats were randomly assigned to either stressed ($n = 8$) or unstressed conditions ($n = 8$). Stressed rats were placed in a small plastic restrainer for 3 h per day for 1 week, a manipulation that produces significant increases in plasma corticosterone levels (Cook & Wellman, 2004). Because the food restriction required for maintenance of bar pressing prevented the use of weight data as a verification of the stress manipulation, a separate group of rats ($N = 8$) with ad lib access to food was restrained for 3 h per day for 1 week. Weight data from these rats were compared to that of unstressed controls ($N = 8$) using a t test.

2.4. Fear conditioning and extinction

One day after the final day of restraint, rats were placed in the operant chambers for a final session of bar press training (VI-60 schedule). During all subsequent phases of training and testing, rats were allowed to bar press for pellets on a VI-60 schedule. Fear conditioning and extinction took place over the following 2 days using a procedure similar to that of Quirk et al. (2000). On day 1, rats were placed in the operant chambers and underwent fear conditioning. After a 3-min acclimation period, rats received five habituation trials consisting of presentation of a 30-s tone (4.5-kHz, 80 db). Rats then underwent fear conditioning, consisting of seven pairings of the tone CS with a footshock US (500-ms, 0.5 mA) co-terminating with the CS. Rats were then returned to their home cages for 1 h, after which they were returned to the chambers and given extinction trials consisting of tone alone. To ensure comparable levels of extinction learning across both groups, on day 1 extinction trials continued until the rat exhibited less than 10% (3 s) freezing on four consecutive trials. The following day, rats were given another 15 extinction trials. For all phases of conditioning and extinction, variable intertrial intervals averaged 4 min, and computer-based operant software (MedPC-IV; Med Associates, St.

Albans, VT) controlled the delivery of tones and shocks. For all trials, the duration of freezing (defined as the absence of any visible movements except that due to breathing) during the tone was measured with a digital stopwatch by an observer blind to experimental conditions. Percent freezing (seconds spent freezing/30 s) during habituation, fear conditioning, extinction on day 1, and extinction on day 2 was calculated and compared across groups using two-way repeated-measures ANOVAS (group \times trial) followed by Bonferroni post hoc comparisons. In addition, trials to criterion on extinction days 1 and 2 were calculated and compared across groups using two-way repeated-measures ANOVAS (group \times extinction session) followed by Bonferroni post hoc comparisons.

3. Results

One week of daily restraint stress significantly attenuated weight gain. By day seven of restraint, average weight of unstressed rats increased to $119.93 \pm 3.45\%$ of their starting weight, whereas in stressed rats, average weight increased to only $107.30 \pm 3.69\%$ of their starting weight ($t(14) = -7.07, p < .05$).

To rule out potential confounds due to differences in activity level between stressed and unstressed groups, average bar presses per min on the days immediately preceding and following chronic restraint were compared across groups using two-way repeated-measures ANOVA (Day \times Group). Although there was no main effect of group on freezing ($F(1, 14) = 1.11, p > .05$), a main effect of day was present ($F(1, 14) = 50.61, p < .05$), with both stressed and unstressed rats pressing at a lower rate following the week of restraint. Although a significant interaction of day and group was present ($F(1, 14) = 5.47, p < .05$), planned comparisons revealed that rate of bar pressing did not differ between unstressed and stressed rats on either the last day of bar press training (Unstressed mean = 10.23 ± 0.84 presses/min, Stressed mean = 10.03 ± 0.90 presses/min; Bonferroni comparison, $p > .05$) or after the final day of restraint (Unstressed mean = 8.34 ± 0.61 presses/min, Stressed mean = 6.31 ± 0.82 bar presses per min; Bonferroni comparison, $p > .05$). Thus, although a trend towards decreased activity in the stressed rats was present, there were no significant differences in activity level across groups.

One week of daily restraint did not significantly influence unconditioned responding to tone alone (Fig. 1A). During the habituation phase, there was no main effect of group on freezing ($F(1, 56) = 1.33, p > .05$) and no interaction of group and trial ($F(4, 56) = 0.82, p > .05$). Likewise, chronic restraint stress did not significantly alter acquisition of the conditioned fear response (Fig. 1B). Overall, percent freezing varied significantly across trials ($F(6, 84) = 10.30, p < .05$), with both groups acquiring the conditioned fear response. No effect of group ($F(1, 84) = 2.23, p > .05$) or interaction of group and trial ($F(6, 84) = 0.91, p > .05$) was present. Thus, by the last acquisition trial, the two groups showed equivalent learning. To further explore the possibility that stressed rats may have acquired the conditioned fear response more rapidly, acquisition data were further analyzed by performing separate analyses on trials 1–4 (before unstressed rats reached

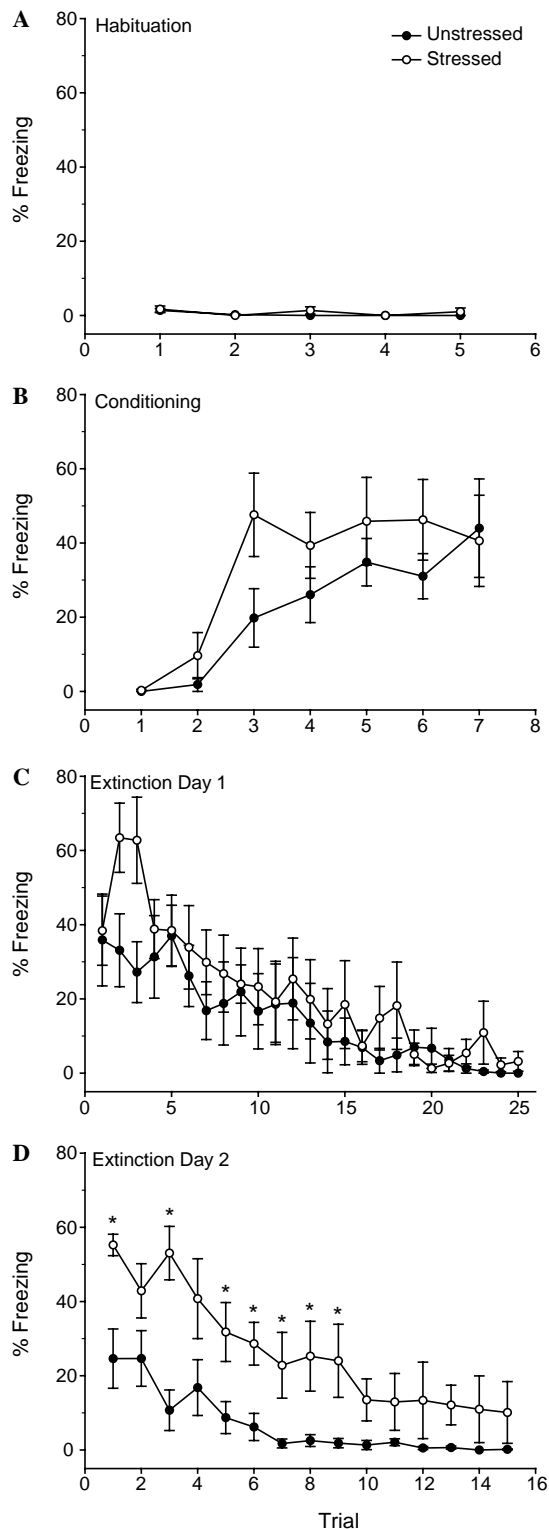


Fig. 1. Mean percent freezing to tone in unstressed (black circles) versus stressed rats (white circles) across habituation (A), conditioning (B), extinction day 1 (C), and extinction day 2 (D) trials. Vertical bars represent SEMs. Asterisk (*) indicates significant difference relative to unstressed rats.

asymptotic performance) and trials 5–7 (after unstressed rats reached asymptotic performance). No significant effect of stress was present during either initial or asymptotic tri-

als (for initial trials, $F(1,39) = 3.00$, $p > .05$; for asymptotic trials, $F(1,26) = 0.24$, $p > .05$), and this did not vary across trials (interaction of group and trial for initial trials, $F(3,39) = 1.64$, $p > .05$; for asymptotic trials, $F(2,26) = 0.59$, $p > .05$). Thus, acquisition of conditioned fear did not vary significantly across the two groups.

During the first extinction phase, as expected, the conditioned fear response diminished with repeated presentations of tone alone (Fig. 1C; for main effect of trial, $F(24,312) = 11.85$, $p < .05$). However, stress did not significantly influence rate of extinction on day 1 (for main effect of group, $F(1,336) = 0.70$, $p > .05$; for interaction of group and trial, $F(24,336) = 1.24$, $p > .05$). Thus, unstressed and stressed rats showed equivalent extinction learning by the end of the first extinction phase.

On the other hand, on extinction day 2, examination of freezing across trials indicated a significant effect of group ($F(1,196) = 12.63$, $p < .05$; Fig. 1D). Although both groups showed a decrease in the conditioned fear response across trials (for main effect of trial, $F(14,196) = 10.06$, $p < .05$; for interaction of group and trial, $F(14,196) = 1.47$, $p > .05$), planned comparisons indicated that stressed rats showed 115% more freezing to the tone on trials 1, 3, and 5 through 9 (Bonferroni comparisons, $p < .05$). However, by trial 10, unstressed and stressed rats showed comparable levels of freezing (for trials 2, 4, and 10–15, all comparisons, $p > .05$).

Analysis of trials to criterion on extinction days 1 and 2 paralleled these findings, with significant effects of both group ($F(1,14) = 6.52$, $p < .05$) and extinction session ($F(1,14) = 9.25$, $p < .05$) and a nonsignificant interaction of group and extinction session ($F(1,14) = 0.80$, $p > .05$; Fig. 2). On extinction day 1, unstressed and stressed rats reached criterion with a mean of 13.38 ± 2.43 and 17.38 ± 2.18 trials, respectively; however, planned comparisons indicated that this 31% difference did not reach significance (Bonferroni comparison, $p > .05$). Alternatively, on extinction day 2, unstressed and stressed rats reached criterion with a mean of 7.50 ± 0.91 and 12.50 ± 1.00 trials, respectively, and this 67% difference was significant (Bonferroni comparison, $p < .05$).

To examine the possibility that the impaired performance on extinction day 2 was due to a stress-induced facilitation of acquisition of the conditioned fear response, two additional analyses were performed. First, a correlational analysis was performed to examine the relationship between performance on either conditioning trial 3 (the trial at which stressed rats appeared to reach asymptotic performance; see Fig. 1B) or conditioning trial 7 and performance on the first trial of extinction day 2. Performance on conditioning trial 3 and 7 was not significantly correlated with performance on the first trial of extinction day 2, either across all animals ($r = .30$ and $-.13$, respectively, $p > .05$; data not shown) or specifically within unstressed ($r = -.10$ and $-.09$, respectively, $p > .05$; data not shown) or stressed rats ($r = .04$ and $-.32$, respectively, $p > .05$; data not shown).

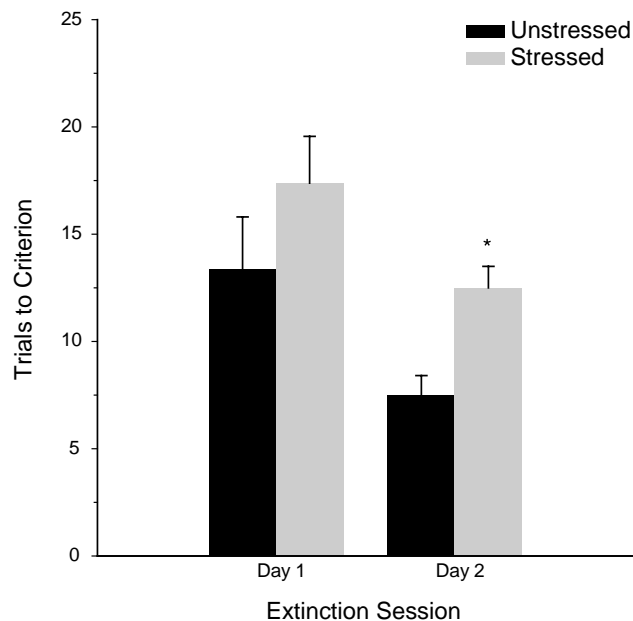


Fig. 2. Although stress did not significantly increase trials to criterion on extinction day 1, it significantly increased trials to criterion on extinction day 2. Mean trials to criterion on extinction days one and two in unstressed (black bars) and stressed (grey bars) rats. Vertical bars indicate SEMs. Asterisk (*) indicates significant difference relative to unstressed rats.

Second, animals were matched for acquisition by excluding stressed rats ($n = 4$) that showed greater than 50% freezing by conditioning trial 3. Performance during habituation, fear conditioning, extinction on day 1, and extinction on day 2 was compared across groups as described above. One week of daily restraint did not significantly influence unconditioned responding to tone alone in animals matched for acquisition (Fig. 3A), with no main effect of group on freezing ($F(1,40) = 3.50, p > .05$) and no interaction of group and trial ($F(4,40) = 1.18, p > .05$) for habituation trials. Similarly, acquisition of the conditioned fear response did not vary across matched groups (Fig. 3B), with no effect of group ($F(1,60) = 0.60, p > .05$) or interaction of group and trial ($F(6,60) = 0.26, p > .05$). Likewise, stress did not significantly influence rate of extinction on day 1 (3C; for main effect of group, $F(1,240) = 1.05, 0 > 0.05$; for interaction of group and trial, $F(24,240) = 1.31, p > .05$). Nonetheless, even when matched for initial acquisition, stressed rats were still impaired during extinction day 2 trials (Fig. 3D; for main effect of group, $F(1,140) = 7.53, p < .05$; for interaction of group and trial, $F(1,140) = 0.95, p > .05$). Planned comparisons demonstrated that stressed rats matched for acquisition showed at least 136% more freezing to the tone on trials 1, 3, 5, 6, 8, 10, and 13 (Bonferroni comparisons, $p < .05$). As in the overall analysis, comparison of trials to criterion for unstressed rats and stressed rats matched for acquisition showed similar trends, with main effects for both group and extinction session ($F(1, 10) = 7.05$ and 6.67 , respectively, $p < .05$). While the interaction of group and extinction session was nonsig-

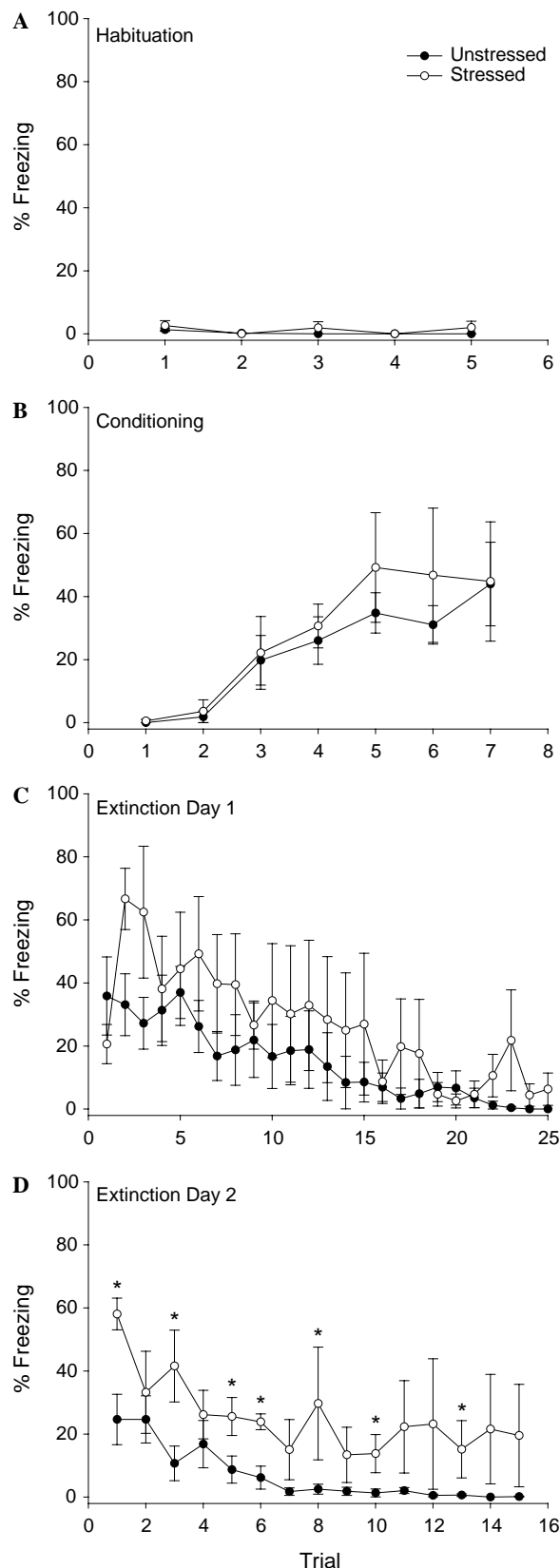


Fig. 3. Mean percent freezing to tone in unstressed (black circles) versus stressed rats (white circles) matched for initial acquisition of the conditioned fear response across habituation (A), conditioning (B), extinction day 1 (C), and extinction day 2 (D) trials. Vertical bars represent SEMs. Asterisk (*) indicates significant difference relative to unstressed rats.

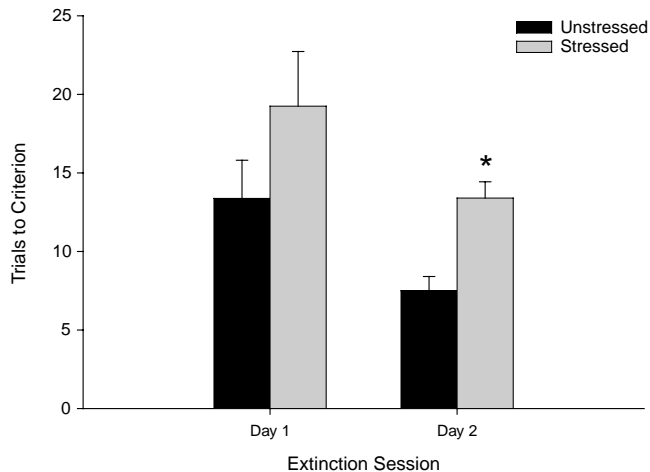


Fig. 4. When controlling for initial acquisition of the conditioned fear response, stress significantly increased trials to criterion on extinction day 2 but not on extinction day 1. Mean trials to criterion on extinction days one and two in unstressed (black bars) and stressed (grey bars) rats matched for initial acquisition. Vertical bars indicate SEMs. Asterisk (*) indicates significant difference relative to unstressed rats.

nificant ($F(1, 10) = 0.19$, $p > .05$), planned comparisons revealed a significant 73% increase in trials required to reach criterion in stressed rats on extinction day 2 only (Fig. 4; Bonferroni comparison, $p < .05$).

4. Discussion

The present study demonstrates a specific effect of one week of restraint stress on recall of extinction of conditioned fear. Chronic stress did not significantly affect unconditioned responding to the tone, acquisition of conditioned fear, or initial extinction. However, 24 h after initial extinction, stressed rats showed markedly attenuated recall of extinction from day one, showing twice as much freezing to the tone as did unstressed rats. This effect on recall of extinction remained after controlling for potential stress-induced facilitation of acquisition of conditioned fear.

The comparability of baseline bar pressing rates across the two groups both before and after chronic stress as well as the specificity of the effect to extinction day 2 suggests that this effect was not due to a general decrease in activity. Similarly, the specificity of the effect to extinction day 2 argues against the possibility that it is due to increased pain sensitivity. Indeed, others (Conrad, LeDoux, Magarinos, & McEwen, 1999) found no effect of chronic restraint stress on pain sensitivity. Thus, the increased freezing on extinction day 2 appears to reflect a stress-induced impairment of recall of extinction.

Alternatively, acute stress can influence nonassociative aspects of behavior temporarily in a time-dependent fashion. Delays of 1–6 h between stressor and testing suppress responses, facilitating passive behaviors, but after 24 h this facilitation does not occur (Anisman, 1975). In the present study, the fear conditioning and extinction commenced 48 h after the last day of restraint. Thus, the increased freezing

on extinction day 2 is not likely due to such time-dependent, nonassociative effects. Nonetheless, this hypothesis could be directly tested by varying the delay between stress and training. For instance, if fear conditioning occurred immediately after restraint, we would expect stressed animals to show facilitated freezing during the first extinction session, which would occur during a 1–6 h delay.

While the acquisition and recall of extinction is, like any complex behavior, dependent on the interaction of many brain systems, a growing body of literature suggests a role for ventral mPFC in recall of extinction. Electrophysiological data have demonstrated that firing of neurons in ventral mPFC is correlated with memory for fear extinction but not acquisition of conditioned fear or initial extinction (Milad & Quirk, 2002), and lesions of ventral mPFC impair recall of extinction while leaving acquisition and initial extinction of conditioned fear intact (Quirk et al., 2000). Furthermore, consolidation of extinction is impaired by blockade of protein synthesis in ventral mPFC (Santini et al., 2004). Our results show a very similar pattern of impairment, with one week of daily stress resulting in a specific deficit in recall of extinction. Thus, stress-induced alterations in dendritic morphology of ventral mPFC (Cook & Wellman, 2004; Radley et al., 2004) could contribute to the deficit in recall of extinction. However, dendritic remodeling is just one of a variety of stress-induced changes seen in mPFC and other structures involved in extinction of conditioned fear. For instance, acute stress increases glutamate (Moghaddam, 1993), dopamine (Abercrombie, Keefe, DiFrischia, & Zigmond, 1989), and acetylcholine release (Mark et al., 1996) in mPFC, and prolongs serotonergic regulation of GABAergic iPSCs in prefrontal pyramidal neurons via activation of PKC (Tan, Zhong, & Yan, 2004). In addition, previous exposure to chronic stress decreases baseline levels of dopamine release in mPFC (Mizoguchi et al., 2000) but sensitizes mPFC dopamine release in response to a novel stressor (Gresch, Sved, Zigmond, & Finlay, 1994). Thus, the stress-induced deficit in recall of extinction as well as stress-induced dendritic changes in mPFC could be due to chronic stress-induced changes in the glutamatergic, monoaminergic, or cholinergic systems in mPFC.

As noted above, ventral mPFC is just one part of the complex neural circuit mediating fear conditioning and extinction. For instance, information about the conditioned stimulus and unconditioned stimulus converges in the lateral amygdala, thought to be the essential site of plasticity in fear conditioning (Fanselow & LeDoux, 1999; LeDoux, 2000). The lateral amygdala projects to the central amygdala, where conditioned fear responses are coordinated via outputs to various brainstem nuclei (LeDoux, 2000). The mPFC likely participates in extinction of conditioned fear by providing inhibitory input to these amygdaloid nuclei (Sotres-Bayon, Bush, & LeDoux, 2004), perhaps via activation of inhibitory neurons in the intercalated nuclei of the amygdala (Berretta, Pantazopoulos, Caldera, Pantazopoulos, & Paré, 2005). In fact, 10

days of chronic immobilization stress results in alterations in dendritic length of projection neurons in the basolateral amygdala (Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002). Immobilization is generally considered to be a more intense stressor than restraint (Vyas et al., 2002). This is consistent with the fact that 10 days of immobilization results in weight loss (Vyas et al., 2002), whereas the restraint-stressed animals used in the present study continued to gain weight, albeit at an attenuated rate. Furthermore, more intense, longer-term chronic restraint stress (6 h/day for 21 days, which produces significant peaks in plasma corticosterone concentrations that continue to occur throughout the duration of the restraint; see Magariños & McEwen, 1995) facilitates fear conditioning (Conrad et al., 1999). The less intense stressor in the present study (3 h/day for just one week) produced changes in recall of extinction but not acquisition of conditioned fear. It is interesting to speculate that the specific effect of stress on recall of extinction in the present study is due to differential effects of stress on brain structures (for instance, medial prefrontal cortex and basolateral amygdala) involved in fear conditioning and extinction. Future studies examining stress-induced changes in fear conditioning and associated changes in relevant brain structures as a function of stress magnitude and duration would clarify this issue.

Acknowledgments

We thank Dale R. Sengelaub and an anonymous reviewer for helpful comments on the manuscript. Supported by MH067607 to C.L.W.

References

- Abercrombie, E. D., Keefe, K. A., DiFrischia, D. S., & Zigmond, M. J. (1989). Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. *Journal of Neurochemistry*, *52*, 1655–1658.
- Anisman, H. (1975). Time-dependent variations in aversively motivated behaviors: nonassociative effects of cholinergic and catecholaminergic activity. *Psychological Review*, *82*(5), 359–385.
- Bagley, J., & Moghaddam, B. (1997). Temporal dynamics of glutamate efflux in the prefrontal cortex and in the hippocampus following repeated stress: Effects of pretreatment with saline or diazepam. *Neuroscience*, *77*(1), 65–73.
- Berretta, S., Pantazopoulos, H., Caldera, M., Pantazopoulos, P., & Paré, D. (2005). Infralimbic cortex activation increases C-Fos expression in intercalated neurons of the amygdala. *Neuroscience*, *132*, 943–953.
- Brown, S. M., Henning, S., & Wellman, C. L. (2005). Short-term, mild stress alters dendritic morphology in rat medial prefrontal cortex. *Cerebral Cortex*, *15*, 1714–1722.
- Conrad, C. D., LeDoux, J. E., Magarinos, A. M., & McEwen, B. S. (1999). Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. *Behavioral Neuroscience*, *113*(5), 902–913.
- Cook, S. C., & Wellman, C. L. (2004). Chronic stress alters dendritic morphology in rat medial prefrontal cortex. *Journal of Neurobiology*, *60*, 236–248.
- Fanselow, M. S., & LeDoux, J. E. (1999). Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala. *Neuron*, *23*, 229–232.
- Gresch, P. J., Sved, A. F., Zigmond, M. J., & Finlay, J. M. (1994). Stress-induced sensitization of dopamine and norepinephrine efflux in medial prefrontal cortex of the rat. *Journal of Neurochemistry*, *63*, 575–583.
- Grudt, T. J., & Perl, E. R. (2002). Correlations between neuronal morphology and electrophysiology features in the rodent superficial dorsal horn. *Journal of Physiology*, *540*, 189–207.
- Jedema, H. P., & Moghaddam, B. (1994). Glutamatergic control of dopamine release during stress in the rat prefrontal cortex. *Journal of Neurochemistry*, *63*(2), 785–788.
- Koch, C., & Segev, I. (2000). The role of single neurons in information processing. *Nature Neuroscience*, *3*, 1171–1177.
- LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience*, *23*, 155–184.
- Lu, Y., Inokuchi, H., McLachlan, E. M., Li, J.-S., & Higashi, H. (2001). Correlation between electrophysiology and morphology of three groups of neurons in the dorsal commissural nucleus of lumbosacral spinal cord of mature rats studied in vitro. *Journal of Comparative Neurology*, *437*, 156–169.
- Magariños, A. M., & McEwen, B. S. (1995). Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: Involvement of glucocorticoid secretion and excitatory amino acid receptors. *Neuroscience*, *69*(1), 89–98.
- Mainen, Z. F., & Sejnowski, T. J. (1996). Influence of dendritic structure on firing pattern in model neocortical neurons. *Nature*, *382*, 363–366.
- Mark, G. P., Rada, P. V., & Shors, T. J. (1996). Inescapable stress enhances extracellular acetylcholine in the rat hippocampus and prefrontal cortex but not the nucleus accumbens or amygdala. *Neuroscience*, *74*, 767–774.
- Meaney, M. J., & Aitken, D. H. (1985). [³H]Dexamethasone binding in rat frontal cortex. *Brain Research*, *328*, 176–180.
- Milad, M. R., & Quirk, G. J. (2002). Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*, *420*, 70–74.
- Mizoguchi, K., Yuzurihara, M., Ishige, A., Sasaki, H., Chui, D.-H., & Tabira, T. (2000). Chronic stress induces impairment of spatial working memory because of prefrontal dopaminergic dysfunction. *Journal of Neuroscience*, *20*(4), 1568–1574.
- Moghaddam, B. (1993). Stress preferentially increases extraneuronal levels of excitatory amino acids in the prefrontal cortex: Comparison to hippocampus and basal ganglia. *Journal of Neurochemistry*, *60*(5), 1650–1657.
- Morgan, M. A., & LeDoux, J. E. (1995). Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Behavioral Neuroscience*, *109*, 681–688.
- Quirk, G. J., Russo, G. K., Barron, J. L., & Lebron, K. (2000). The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *Journal of Neuroscience*, *20*(16), 6225–6231.
- Radley, J. J., Sisti, H. M., Hao, J., Rocher, A. B., McCall, T., Hof, P. R., et al. (2004). Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. *Neuroscience*, *125*(1), 1–6.
- Rall, W., Burke, R. E., Holmes, W. R., Jack, J. J., Redman, S. J., & Segev, I. (1992). Matching dendritic neuron models of experimental data. *Physiological Reviews*, *72*, S159–S186.
- Santini, E., Ge, H., Ren, K., de Ortiz, S. P., & Quirk, G. J. (2004). Consolidation of fear extinction requires protein synthesis in the medial prefrontal cortex. *Journal of Neuroscience*, *24*(25), 5704–5710.
- Sotres-Bayon, F., Bush, D. E. A., & LeDoux, J. E. (2004). Emotional perseveration: an update on prefrontal–amygdala interactions in fear extinction. *Learning and Memory*, *11*, 525–535.
- Tan, H., Zhong, P., & Yan, Z. (2004). Corticotropin-releasing factor and acute stress prolongs serotonergic regulation of GABA transmission in prefrontal cortical pyramidal neurons. *Journal of Neuroscience*, *24*(21), 5000–5008.
- Vyas, A., Mitra, R., Shankaranarayana Rao, B. S., & Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *Journal of Neuroscience*, *22*(15), 6810–6818.