



Chronic stress and sex differences on the recall of fear conditioning and extinction

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ABSTRACT

Chronic stress effects and sex differences were examined on conditioned fear extinction. Male and female Sprague–Dawley rats were chronically stressed by restraint (6 h/d/21 d), conditioned to tone and footshock, followed by extinction after 1 h and 24 h delays. Chronic stress impaired the recall of fear extinction in males, as evidenced by high freezing to tone after the 24 h delay despite exposure to the previous 1 h delay extinction trials, and this effect was not due to ceiling effects from overtraining during conditioning. In contrast, chronic stress attenuated the recall of fear conditioning acquisition in females, regardless of exposure to the 1 h extinction exposure. Since freezing to tone was reinstated following unsignalled footshocks, the deficit in the stressed rats reflected impaired recall rather than impaired consolidation. Sex differences in fear conditioning and extinction were observed in nonstressed controls as well, with control females resisting extinction to tone. Analysis of contextual freezing showed that all groups (control, stress, male, female) increased freezing immediately after the first tone extinction trial, demonstrating contextual discrimination. These findings show that chronic stress and sex interact to influence fear conditioning, with chronic stress impairing the recall of delayed fear extinction in males to implicate the medial prefrontal cortex, disrupting the recall of the fear conditioning acquisition in females to implicate the amygdala, and nonstressed controls exhibiting sex differences in fear conditioning and extinction, which may involve the amygdala and/or corticosterone levels.

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1. Introduction

Chronic stress alters neuronal dendritic morphology and function in a number of brain regions involved in cognition. Chronic stress reduces dendritic arbors in the hippocampus (Baran et al., 2005; Magariños, McEwen, Flügge, & Fuchs, 1996; McLaughlin, Gomez, Baran, & Conrad, 2007a; Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002; Watanabe, Gould, & McEwen, 1992) and prefrontal cortex (PFC, Brown, Henning, & Wellman, 2005; Cook & Wellman, 2004; Izquierdo, Wellman, & Holmes, 2006; Radley et al., 2005), and these morphological alterations correspond with impaired hippocampal-dependent spatial ability (Kleen, Sitomer, Killeen, & Conrad, 2006; Luine, Villegas, Martinez, & McEwen, 1994; McLaughlin et al., 2007a; Park, Campbell, & Diamond, 2001; Wright & Conrad, 2005) and PFC-dependent recall of conditioned fear extinction (Garcia, Spennato, Nilsson-Todd, Moreau, & Deschaux, 2008; Miracle, Brace, Huyck, Singler, & Wellman, 2006), respectively. Chronic stress also enhances dendritic arborization in the amygdala (Vyas et al., 2002) and facilitates amygdala-dependent emotionally salient events such as acquisition of fear conditioning (Conrad, Magariños, LeDoux, & McEwen, 1999;

Conrad, Mauldin-Jourdain, & Hobbs, 2001). These studies demonstrate that chronic stress influences dendritic morphology, which appears to impact function in a variety of brain regions.

The aforementioned studies used male subjects, but chronic stress influences dendritic morphology and function in females differently than in males. Compared to chronically stressed males, chronically stressed females show mild dendritic retraction in the CA3 region of the hippocampus (Galea et al., 1997), which is exacerbated by ovariectomy (McLaughlin, Baran, Wright, & Conrad, 2005). However, chronic stress fails to impair hippocampal-dependent spatial ability in females to the same extent as previously reported in males (Bowman, Zrull, & Luine, 2001; Conrad, Grote, Hobbs, & Ferayorni, 2003a). Specifically, chronically stressed females show delayed spatial navigation, which is maintained longer than nonstressed controls (Conrad et al., 2003a), and may involve interactions with novelty (Frye, 1995) and/or perseveration tendencies of sustained interest (Baran et al., 2002; Conrad et al., 2003a). Perseveration is a disruption of behavioral inhibition and involves the PFC (Squire et al., 2003). Given the recent evidence that chronic stress decreases PFC dendritic complexity in females (Garrett & Wellman, 2006), chronic stress may influence cognition in females through PFC-mediated functions.

The current study examined the impact of chronic stress on PFC function in male and female rats using PFC-dependent conditioned fear extinction recall. Previous research shows medial PFC lesions

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in male rats impair conditioned fear extinction recall after a 24 h delay (Quirk, Russo, Barron, & Lebron, 2000) and that chronic stress causes a similar deficit in male rats (Garcia et al., 2008; Miracle et al., 2006). However, it is unclear whether overtraining contributed to ceiling effects, which could have produced the previously described chronic stress deficit in males (Garcia et al., 2008; Miracle et al., 2006). The following study will be the first to utilize a modified version of the fear extinction recall task to test the effect of chronic stress on PFC function in both male and female rats and incorporating control groups to investigate potential ceiling and/or nonassociative effects. We hypothesized that chronic stress and sex differences will influence recall of conditioned fear extinction.

2. Materials and methods

2.1. Subjects

One hundred four, female and male Sprague–Dawley rats (60 females weighed approximately 250 g upon arrival with 44 males age-matched to females; Charles River Laboratories) were housed in light and sound attenuating chambers on a 12:12 light cycle (lights off at 6 AM) according to conditions specified by the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources on Life Science, National Research Council, 1996). Food and water were administered *ad libitum*. Behavioral testing occurred during the dark phase of the light cycle.

2.2. Chronic stress by restraint

After one week acclimation to the facilities at ASU, rats were weighed and placed into either a control or chronic stress group. Rats in the chronic stress group were then placed in wire mesh restrainers (16.5 cm diameter × 24.1 cm long; 19.1 cm diameter × 26.7 cm long as the rats grew) for 6 h per day for 21 days. Rats were returned to their home cages during restraint, a procedure consistent with previous research (Conrad, Grote, Hobbs, & Ferayorni, 2003b; Magariños & McEwen, 1995; McLaughlin, Gomez, Baran, & Conrad, 2007b). Control rats were undisturbed during the restraint period. Restraint occurred during the dark phase of the light cycle.

2.3. Fear conditioning

2.3.1. Apparatus

Rodent fear conditioning chambers (25 cm depth × 29 cm height × 26 cm width: Coulbourn Instruments, E10-18TC) were contained in sound-attenuating cubicles (Coulbourn, E10-23, white). A PC interface card (Coulbourn, L18-16S/C), a universal link (Coulbourn, L91-04S), and Winlinc software (v 1.1, Coulbourn, D91-04) controlled the stimulus presentation. A frequency generator (Coulbourn, E12-01) produced a tone (75 dB, ~3.0 kHz) through

a speaker located in the side panel of the conditioning chamber. The shock (500 ms, 0.5 mA, Coulbourn Animal Shock Generator, E13-14) was a current, equally distributed through a metal grid floor (Coulbourn, E10-18RF). Behavior was videotaped for analysis using a camera (Coulbourn, E27-01) mounted on the ceiling. Infrared lights (Coulbourn, E27-91) located on the side panels of the chamber denoted the onset and offset of the tone, since there was no audio on the videotaped recordings. The infrared lights were undetectable to the rats. A house light (Coulbourn, E11-01) mounted in the side panel illuminated the chamber. The fear conditioning chambers were cleaned with 95%-ethanol each time a rat was removed from the chamber.

2.3.2. Procedure

This procedure was adapted from Quirk et al. (2000). In that study, both lever pressing and freezing to tone were utilized to assess fear extinction recall. Since both measures portrayed similar recall of fear extinction, we incorporated a paradigm that measured freezing only. A timeline of the study is presented in Table 1. Fear conditioning was conducted over three days beginning one day after the end of restraint. The transport of rats to the fear conditioning chamber occurred in the rats' home cages.

On day 0 (acclimation), rats were placed in the fear conditioning chamber for 10 min. Following acclimation, the rats were returned to the colony room.

On day 1 (habituation, conditioning, 1-h delay extinction), control and chronically stressed rats were placed in the fear conditioning chambers and given five habituation trials consisting of 30 s tones to slow acquisition during conditioning and to reduce the likelihood for chronic stress to potentiate acquisition, as we found previously (Conrad et al., 1999; Conrad et al., 2001). Immediately following the habituation trials, seven conditioning trials occurred in which the completion of a 30 s tone was immediately paired with a footshock. The habituation and conditioning trials lasted approximately 1 h. After the conditioning trials, the rats were transported to the colony room for 1 h before being returned to the chambers. Rats were then given 15 extinction trials consisting of 30 s tones without footshock. The extinction trials lasted approximately 1 h. The average inter-trial interval (ITI) during each exposure to tone only (habituation, extinction) or tone and footshock pairings (training) was 4 min, with a range of 2–6 min.

On day 2 (24-h delay extinction), rats were given another 15 extinction trials. Immediately following these trials, two unsignalled footshocks were administered to reinstate extinguished conditioned freezing responses, followed by another 15 extinction trials. Previous studies show that unsignalled shocks partially reinstate extinguished conditioned responses and that reinstatement quickly extinguishes, which suggests that reinstatement is due to a previously conditioned association instead of a sensitization ef-

Table 1
Timeline and treatment conditions.

Group	Week 1	Week 2–4	Week 5	
			Extinction day 1	Extinction day 2
<i>Paired</i>				
Control	Arrival	Restraint	Habituation, fear conditioning (paired), and extinction	Extinction
Chronic stress				
<i>Unpaired</i>				
Control	Arrival	Restraint	Habituation, fear conditioning (unpaired), and extinction	Extinction
Chronic stress				
<i>Day 1 extinction naïve</i>				
Control	Arrival	Restraint	Habituation, fear conditioning (paired), and no extinction	Extinction
Chronic stress				

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