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## Research Report

# Early life stress impairs fear conditioning in adult male and female rats

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#### Abbreviations:

PN, postnatal

C, control

BS, brief maternal separation

PS, prolonged maternal separation

M, male

F, female

USV, ultrasonic vocalizations

### ABSTRACT

We demonstrated that neonatal isolation (1-h pup isolation; postnatal days 2–9) impairs context-induced fear conditioning in adult male rats and tends to enhance this effect and foot shock sensitivity in females. In this study, we examine the effects of brief (i.e., handling; 15 min) and prolonged (3 h) maternal separations (postnatal days 1–21) on fear conditioning and foot shock sensitivity in adult male and female rats. Identical training and test conditions from our prior study were employed so comparisons of the three early life stressors could be made. Context- and cue-elicited freezing and ultrasonic vocalizations (USVs; 22 kHz) were measured after 10 tone-shock training trials in Experiment 1. In Experiment 2, foot shock responses (flinch, jump, sonic vocalizations) to escalating shock levels were assessed. Brief maternal separation impaired context- and cue-conditioned fear in rats of both sexes as assessed by USVs. Prolonged maternal separation only impaired context fear in female rats. There were no effects on foot shock sensitivity. Results of this and other studies suggest that early life stress impairs fear conditioning in adult rats whereas stress experienced in adulthood has the opposite effect. These opposing effects may reflect developmental differences on stress-induced alterations on hippocampal regulation of the hypothalamic–pituitary–adrenal axis.

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## 1. Introduction

Clinical studies indicate that early adverse events enhance the risk of developing behavioral disorders in adulthood (Heim and Nemeroff, 2001; Kendler et al., 2000; Yehuda et al., 2001). There are difficulties in determining clear causal effects of early life stress on adult behavior in humans, but research in animals could provide valuable information because it allows

control over many variables. Indeed, much research over the past several decades has examined the long-term neuroendocrinological and behavioral consequences of early life stress in rats. Initial studies, conducted by Levine and Denenberg and their colleagues, assessed the effects of “handling”, the brief (e.g., 15 min) removal of rat pups from the dam during early postnatal life, on stress responsiveness, and behaviors indicative of anxiety or fear (Denenberg, 1964; Levine, 1956). A

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number of studies have also examined the effects of the more prolonged (e.g., 3 or more hours) removal of the pups from the dam known as maternal separation (Lehmann and Feldon, 2000; Meaney et al., 1996; Plotsky and Meaney, 1993; Pryce and Feldon, 2003). Although it has been suggested that maternal separation has neuroendocrinological and behavioral effects that are the opposite of handling (Francis et al., 1999), other research conflicts with this notion (Lehmann and Feldon, 2000; Macri et al., 2004; Pryce and Feldon, 2003). We have examined the effects of another early life stress, neonatal isolation, in which rat pups are isolated individually for 1 h per day on postnatal days 2–9 (Kehoe and Shoemaker, 2001; Kosten and Kehoe, 2005). We find that neonatal isolation enhances acquisition of cocaine self-administration in male and female rats (Kosten et al., 2000, 2004). How neonatal isolation compares to handling and maternal separation is unclear, in part, because several parameters and procedures vary across studies and laboratories. Some parametric differences include strain, age, and sex of rats as well as duration and numbers of postnatal separations.

Nonetheless, numerous studies show that adult rats with handling experience show attenuated unconditioned fear as evidenced by decreased activity levels in an open field relative to non-handled control rats (Caldji et al., 2000; Gilad et al., 2000; Ploj et al., 1999; Vallee et al., 1997; VonHoersten et al., 1993). Handling is also associated with reduced anxiety in adult rats as evidenced by increased entries in open arms of an elevated plus maze (McIntosh et al., 1999; Meerlo et al., 1999; Ploj et al., 1999). However, some studies report no effects of handling on these adult behaviors (Boccia and Pedersen, 2001; Durand et al., 1998; Meerlo et al., 1999; Pryce et al., 2001a). The effects of maternal separation on unconditioned fear and anxiety have also been assessed. Maternal separation decreases fear in young rats (30–40 days old) (Suchecki et al., 2000; VonHoersten et al., 1993) but has no effect in adult rats in most studies (Lehmann et al., 1999; Marmendal et al., 2004; Pryce et al., 2001b; Shalev and Kafkafi, 2002). Yet, some reports suggest that maternal separation increases unconditioned fear in adult rats (Kalinichev et al., 2002a; Ogawa et al., 1994). Maternal separation increases anxiety in the elevated plus maze in some cases (Kalinichev et al., 2002b; Wigger and Neumann, 1999) but is reported to have no effect in other studies (Boccia and Pedersen, 2001; Lehmann et al., 1999). Finally, our research with neonatal isolation has consistently failed to show any effect on unconditioned fear (Kehoe et al., 1998; Kosten et al., 2000, 2004, 2005).

Conditioned fear can be assessed by administering foot shocks in a distinctive context and measuring behavioral or stress hormone responses to the subsequent presentation of the shock-paired context. In addition to context-induced fear, foot shocks can be paired with a discrete tone cue and responses to subsequent cue presentations assessed. Prior research shows that context fear conditioning, assessed by increased freezing behavior, is impaired in adult rats with handling experience (Meerlo et al., 1999) but is enhanced in juvenile rats handled as pups (Beane et al., 2002). Maternal separation for 24 h on either postnatal day 9 or 18 tends to decrease context fear in male rats with no effect in female rats and 24 h maternal separation on postnatal day 4 tends

to decrease cue-induced fear in rats of both sexes (Lehmann et al., 1999). Cue-induced corticosterone levels are reduced in male rats with brief (15 min) neonatal isolation and in female rats with prolonged (4 h) neonatal isolation (Pryce et al., 2003). Our recent study also shows sex-specific effects of 1-h neonatal isolation on context-induced fear with no effect on cue-induced fear (Kosten et al., 2005). Adult male rats with neonatal isolation experience show impaired context-induced ultrasonic vocalizations (USV) whereas adult female rats tend to show an enhanced response to the context. The tendency for enhanced context-induced fear in female rats may reflect the tendency for neonatal isolation to enhance foot shock sensitivity in rats of this sex.

The purpose of the present study was to investigate the effects of brief (15 min; e.g., handling) and prolonged (3 h) maternal separation on fear conditioning in adult male and female rats in order to compare results to our prior study with neonatal isolation (Kosten et al., 2005). Fear conditioning was performed in the same manner as our previous study and employed rats of both sexes and of the same strain (Sprague–Dawley). Conditioned fear responses to discrete cue and background contextual stimuli were assessed via freezing and 22 kHz USV (Kosten et al., 2005; Lee et al., 2001). Our prior study with neonatal isolation showed some effect on sensitivity to foot shock. Differences in foot shock sensitivity could affect the strength of fear conditioning. Thus, we also examined this unconditioned effect in the present study.

## 2. Results

### 2.1. Experiment 1: fear conditioning

#### 2.1.1. Acquisition

Fig. 1A depicts the mean percentage freezing during 10 tone-shock training for M-C, M-BS, M-PS, F-C, F-BS, and F-PS groups (male and female groups are plotted separately for the purpose of clarity). As shown, none of the groups exhibited freezing during the first minute of baseline prior to tone-footshock presentations. Subsequent to tone-footshock pairings, however, animals in all 6 groups exhibited robust postshock freezing,  $F(10,340) = 62.87$ ,  $P < 0.01$ . There was no reliable main effect of either maternal separation or sex. However, there was a marginal interaction effect between maternal separation and sex,  $F(2,34) = 2.70$ ,  $P = 0.08$ , which is likely due to females, but not males, in PS groups displaying lower postshock freezing compared to controls. Fig. 1B depicts the mean percentage of USV duration exhibited by animals during tone-shock training. Animals in all 6 groups exhibited robust postshock USV during training,  $F(10,340) = 75.34$ ,  $P < 0.01$ . However, not all groups displayed postshock USV with the same rate as shown by the significant interaction effect of trial  $\times$  maternal separation  $\times$  sex,  $F(20,340) = 2.06$ ,  $P < 0.01$ . Furthermore, there was a main effect of maternal separation,  $F(2,34) = 3.42$ ,  $P < 0.05$ , as well as sex,  $F(1,34) = 5.65$ ,  $P < 0.05$ . These results are due to females, but not males, in BS and PS groups showing lower levels of USV compared to controls.

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