Brief Communication

Selective enhancement of fear learning and resistance to extinction in a mouse model of acute early life trauma

Elizabeth A. Sneddon, Collin A. Riddle, Kristen M. Schuh, Jennifer J. Quinn, and Anna K. Radke

Department of Psychology, Center for Neuroscience and Behavior, Miami University, Oxford, Ohio 45056, USA

Early life stress (ELS) experiences can cause changes in cognitive and affective functioning. This study examined the persistent effects of a single traumatic event in infancy on several adult behavioral outcomes in male and female C57BL/6J mice. Mice received 15 footshocks in infancy and were tested for stress-enhanced fear learning, extinction learning, discrimination and reversal learning, and novel object recognition. Infant trauma potentiated fear learning in adulthood and produced resistance to extinction but did not influence other behaviors, suggesting restricted effects of infant trauma on behaviors reliant on cortico-amygdala circuitry.

Exposure to traumatic events early in childhood is associated with the development of psychiatric disorders (Copeland et al. 2018) and deficits in cognitive and affective functioning (Pechtel and Pizzagalli 2011) in adulthood. In humans, early life stress (ELS) is defined as experiencing traumatic events in childhood (Pechtel and Pizzagalli 2011). Rodent models of ELS suggest that acute versus chronic stress may differentially alter systems that regulate the stress response, producing different behavioral outcomes in adulthood (Pryce et al. 2002; Musazzi et al. 2017).

Stress-enhanced fear learning (SEFL), a powerful preclinical model of PTSD- and addiction-like behaviors, captures the enduring, maladaptive effects of a single traumatic event on behavior (Rau et al. 2009; Meyer et al. 2013; Radke et al. 2019). In these studies, exposure to 15 footshocks enhances contextual fear conditioning later in life. For infant SEFL, enhanced contextual fear conditioning occurs months after the initial stressful experience and in the absence of memory for the context in which ELS was experienced (Poulos et al. 2014; Quinn et al. 2014). SEFL protocols have been used to model adult or infant trauma in rats (e.g., Rau et al. 2009; Poulos et al. 2014; Quinn et al. 2014) and have been extended to adult mice (Sillivan et al. 2017; Hassien et al. 2020; Pennington et al. 2020). However, to our knowledge, no studies have established the use of acute, infant footshock as a model of ELS in mice.We sought to characterize the effects of acute, infant trauma exposure across several types of learning in adult mice. We tested mice exposed to 15 footshocks on postnatal day (PND) 17 for contextual fear learning, extinction of fear, discrimination and reversal learning, and novel object recognition. Our results suggest that exposure to acute infant trauma enhances fear learning and resistance to extinction in adulthood, but does not alter other types of learning.

Male and female C57BL/6J mice were generated from breeding pairs from The Jackson Laboratory. Mice were group-housed (two to four mice/cage) post-weaning and were provided food and water ad libitum, unless otherwise specified. Mice were on a 12:12 light/ dark cycle. Other than trauma exposure, all behavioral tests were conducted during adulthood (PND 60+). Animals were cared for in accordance with the guidelines set by the National Institutes of Health and all procedures were approved by the Institutional Animal Care and Use Committee at Miami University.

We first established that exposure to infant footshock produces enhanced contextual fear conditioning in adulthood. Mice were placed in a MED-Associates conditioning chamber (context A) on PND 17 (Fig. 1A; after Quinn et al. 2014). Context A was brightly lit, contained a uniform grid floor, was scented with vanilla (50%), and was cleaned with odorless 5% sodium hydroxide. Mice received either 0 or 15 footshocks (1 mA, 1 sec) during a 60-min session beginning 180 sec following placement in the chamber. Progressive scan video cameras containing visible light filters monitored mice throughout the session. Video Freeze software (Med Associates, Inc.) analyzed the video and data were expressed as percent of time spent freezing during the session. Fear conditioning experiments were powered to detect sex differences with an n of eight per sex. Because differences were not observed when sex was included as a factor in analyses, all reported results represent data from both sexes. Due to computer malfunction, fear conditioning sessions from 14 mice were hand scored according to standard time-sampling procedures (Chowdhury et al. 2005) and data from three mice had to be excluded on extinction session 2.

Contextual fear conditioning occurred on PND 60 in a novel context (context B). Context B was dark with a staggered grid floor and cleaned and scented with acetic acid (5%). Baseline freezing during the first 180 sec in this novel context was assessed and used to measure generalization between the stress exposure context (context A) and the novel fear conditioning context (context B). Mice received either 0 or 1 footshocks (1 mA, 1 sec) 180 sec into a 3.5-min session. Thus, there were four groups (infant trauma/adult fear conditioning): no/no shock, $n = 14$; 15/no shock, $n = 15$; no/one shock, $n = 15$; and 15/one shock, $n = 18$. To test extinction of fear memory, mice were reintroduced to context B for two 8-min sessions, separated by 24 h. Finally, mice were reintroduced to context A for an 8-min retention test of the original context.

Mice exposed to 15 footshocks in infancy and conditioned with one footshock as adults exhibited robust SEFL. There were

Corresponding author: aradke@miamioh.edu
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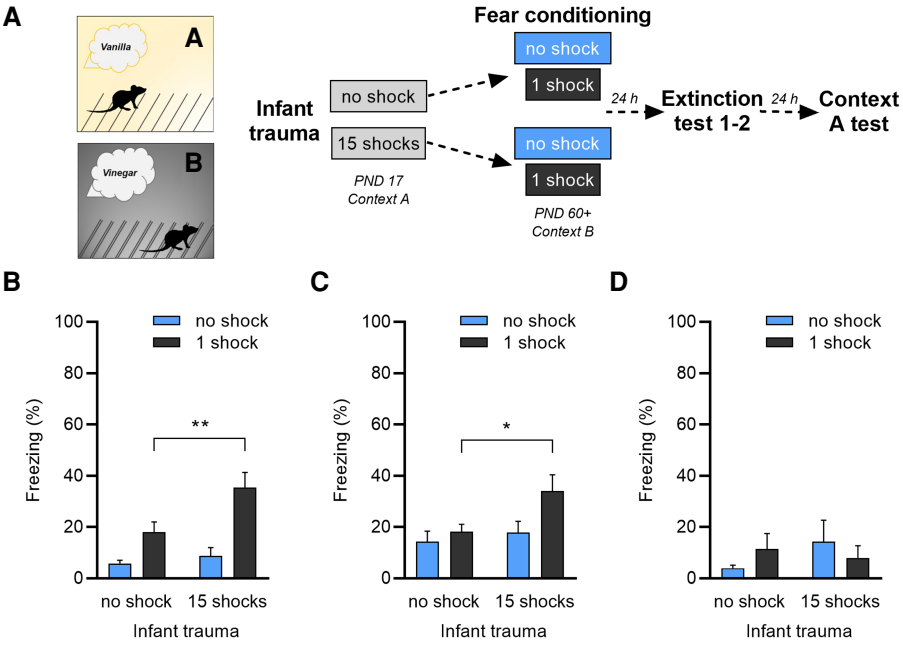

Figure 1. Acute infant trauma produces stress-enhanced fear learning in adulthood. (*A*) Experimental timeline and visual representation of context A and context B. Infant trauma consisted of 15 footshocks or no footshocks on PND 17 in context A. Adult fear conditioning consisted of one footshock (black bars) or no footshock (blue bars) on PND 60 in context B. Extinction was assessed in context B. Memory of the infant trauma was assessed in context A. Stress enhanced fear learning (SEFL) was observed in mice who were exposed to early life stress (15 shocks) and fear conditioning (one shock) for extinction test 1 (*B*) and extinction test 2 (*C*). (*) $P<0.05$, (**) $P<0.01$ versus no/one shock group (Holm–Sidak test). (*D*) Mice showed little freezing, indicating an absence of fear memory for the infant trauma in context A. Data are means ± SEM.

no differences in baseline freezing during the adult fear conditioning session (infant trauma: $F_{(1,47)}=2.67$, $P=0.109$, no/no shocks = 0.26 ± 0.15; no/one shock = 2.17 ± 0.64; 15/no shocks = 2.14 ± 0.76; 15/one shock = 7.17 ± 3.25; all data mean ± SEM). For extinction sessions (Fig. 1B,C), a mixed-effects analysis identified main effects of trauma ($F_{(1,58)}=5.68$, $P=0.020$), fear conditioning ($F_{(1,58)}=12.40$, $P<0.001$), and session ($F_{(1,55)}=5.25$, $P=0.026$). There was a significant interaction between fear conditioning and session ($F_{(1,55)}=7.10$, $P=0.010$). Two-way ANOVA was next used to examine each test session. For session 1 (Fig. 1B), there were main effects of trauma ($F_{(1,58)}=5.72$, $P=0.020$) and fear conditioning ($F_{(1,58)}=21.10$, $P<0.001$). The interaction of trauma and fear conditioning did not reach the threshold for significance ($F_{(1,58)}=2.87$, $P=0.096$). Follow-up Holm Sidak's tests revealed that adult fear conditioning produced greater freezing in mice exposed to infant footshock vs. trauma-naïve mice ($P=0.008$). For the second extinction test (Fig. 1C), the main effects of trauma ($F_{(1,55)}=3.72$, $P=0.059$) and fear conditioning ($F_{(1,55)}=3.92$, $P=0.053$) approached the threshold for significance. Follow-up Holm Sidak's tests revealed that trauma-exposed mice froze more than trauma-naïve mice following adult fear conditioning only ($P=0.042$). When tested for memory of the context used for trauma-exposure on PND 17 (context A), mice demonstrated minimal freezing and two-way ANOVA found no significant main effects or interactions (Fs < 1.39) (Fig. 1D). Percent freezing in infancy and in extinction test 1 in adulthood were correlated ($r=-0.481$, $P=0.043$) for the 15/one group alone. Activity bursts in infancy did not correlate with freezing behavior in adulthood. These results indicate that mice exposed to infant trauma who experienced fear conditioning in adulthood exhibited SEFL on the first and second extinction sessions but the memory of the trauma experience was not retained into adulthood.

Since PTSD is associated with deficits in fear extinction (Zuj et al. 2016), we next examined extinction learning using 30-min sessions (Fig. 2A). Mice were exposed to acute infant trauma (0 or 15 footshocks) on PND 17. On PND 60, mice were reintroduced to context A for an 8-min test of memory for the original ELS context prior to fear conditioning (no/one shock = 2.41 ± 0.58; 15/one shock = 3.50 ± 0.42; no/three shocks = 1.86 ± 0.43). On PND 61 fear conditioning occurred in context B. Since we observed that trauma-naïve mice displayed very little fear conditioning following one footshock (Fig. 1B,C), mice in this experiment received either one or three footshocks during adult fear conditioning. There were three groups (infant trauma/adult fear conditioning): no/one shock, $n=17$; 15/one shock, $n=17$; no/three shocks, $n=18$. Retention of fear memory was tested for five subsequent days (PND 62–66) in context B during 30-min sessions.

On the first extinction session, there were significant main effects of time ($F_{(29,1421)}=2.23$, $P<0.001$) and group ($F_{(2,49)}=3.54$, $P=0.037$) and a significant interaction ($F_{(58,1421)}=1.93$, $P<0.001$). Holm–Sidak follow-up comparisons revealed that trauma-exposed mice (15/one shock) and mice conditioned with three footshocks during adulthood (no/three shocks) froze more than the no/one shock group during the first 3 min ($P<0.05$ for minute 1 and $P<0.01$ for minutes 2 and 3) of the first extinction session (Fig. 2B). Trauma-exposed mice continued to freeze more than the no/one shock group during minutes 4–7 ($P<0.01$) and minute 11 ($P<0.05$). Freezing in the no/3 shocks group was similar to trauma-exposed mice for the first 4 min but diminished sooner, evidenced by a significant difference between these groups during minutes 5, 6, and 9 ($P<0.05$). These results suggest that conditioning with three footshocks produces similar levels of fear in trauma-naïve mice as conditioning with one footshock in trauma-exposed mice, but that within-session extinction is delayed in the trauma-exposed group.

To examine extinction across the five sessions, we averaged freezing during the first 8 min of each session. We found significant main effects of session ($F_{(4,196)}=22.92$, $P<0.001$) and group ($F_{(2,49)}=6.38$, $P=0.003$) and a significant interaction ($F_{(8,196)}=2.75$, $P=0.007$). Holm–Sidak follow-up comparisons revealed that mice exposed to infant trauma (15/one shock) and mice in the no/three shock group froze more than those in the no/one shock group on extinction session 1 ($P<0.01$ and $P<0.05$, respectively) (Fig. 2C). On session 2, freezing was greater in trauma-exposed mice versus both other groups ($P<0.01$). Percent freezing in infancy did not correlate with freezing behavior in adulthood. Activity bursts in infancy correlated with freezing behavior in adulthood on extinction test 1 ($r=-0.558$, $P=0.020$). These results further suggest that infant trauma produces resistance to extinction.

To determine whether the behavioral alterations observed in mice exposed to infant trauma extend to other types of learning, we tested the effects of infant footshock on operant discrimination and reversal learning for food reward and novel object recognition. For discrimination and reversal learning, we used a subset of mice

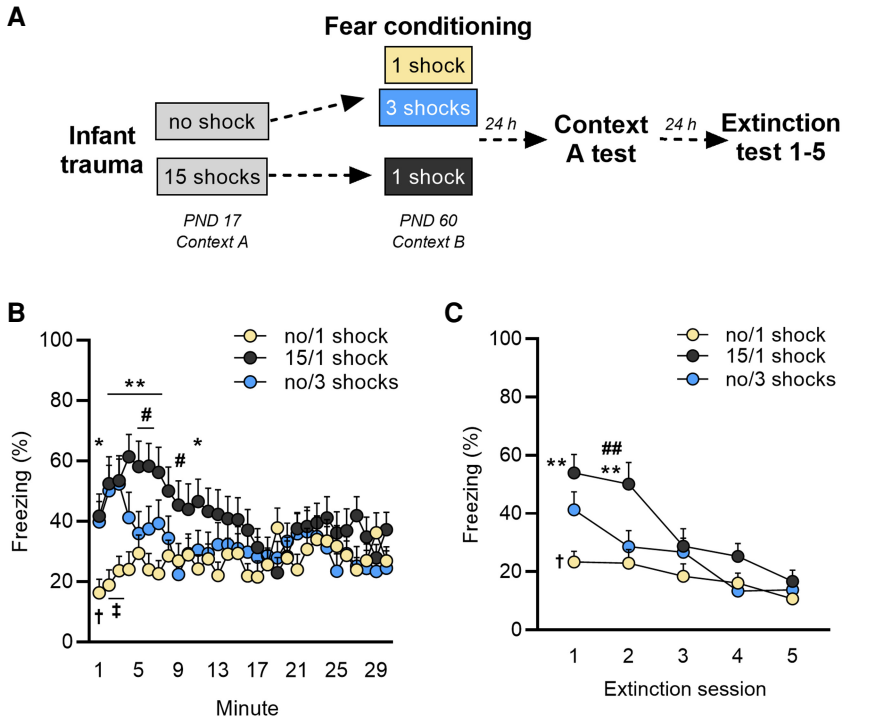

Figure 2. Extinction of fear learning is impaired following acute infant trauma. (*A*) Experimental timeline. Infant trauma consisted of 15 footshocks or no footshocks on PND 17 in context A. Adult fear conditioning consisted of one (yellow symbols) or three (blue symbols) footshocks in trauma-naïve mice and one footshock (black symbols) in trauma-exposed mice in context B. Memory of the infant trauma was assessed in context A. Mice received five extinction sessions in context B. (*B*) On extinction day 1, trauma-exposed mice initially froze at the same level as trauma-naïve mice conditioned with three footshocks but fear persisted longer, demonstrating within-session resistance to extinction. (*) $P<0.05$, (**) $P<0.01$ 15/one shock group versus no/one shock group; ($^{\#}$) $P<0.05$ 15/one shock group versus no/three shocks group; (†) $P<0.05$, (‡) $P<0.01$ no/one shock group versus no/three shock group (Holm–Sidak test). (*C*) Freezing was averaged across the first 8 min of each extinction session. Trauma-exposed mice demonstrated resistance to extinction across sessions. On session 1, both trauma-exposed (15/one shock group) and mice conditioned with three footshocks (no/three shock group) had elevated freezing compared to mice conditioned with one footshock. On session 2, freezing in trauma-exposed mice remained elevated and was greater than in the other two groups. (**) $P<0.01$ 15/one shock group versus no/one shock group. ($^{\#\#}$) $P<0.01$ 15/one shock group versus no/three shocks group. (†) $P<0.05$ no/one shock group versus no/three shocks group (Holm–Sidak test). Data are means ± SEM.

from the first experiment (no shock = 20, 15 shocks = 17) restricted to 85% of free-feeding weight. Mice underwent one habituation day with ten 14-mg grain pellets (Bio Serv) in their home cages. The following day, mice began 15-min training sessions in a standard mouse operant chamber (Med Associates). There were two nose-poke holes and a reward receptacle on one wall of the chamber and a house light and speaker on the opposite wall. The chamber was housed in a sound and light-attenuating box and connected to a computer for data collection (Med-PC V software suite). For all sessions, the house light was off and lights in the nose-poke holes were on. Following a correct response, a 2-sec, 65-dB tone sounded and there was a timeout period of 20 sec following reward delivery during which the lights above the nose-poke holes were off and no rewards could be earned.

During the first session, 30 pellets were automatically delivered into the reward receptacle. Next, mice were trained to respond for the food reward on a fixed ratio 1 (FR1) schedule by responding at either nose-poke hole until meeting criterion of 30 responses in 15-min. For discrimination, mice were trained to respond at the active nose-poke hole (100% probability of reward), which was randomly assigned to the left or right side. The contingencies of the active and inactive nose-pokes holes were reversed once criterion was met (≥30 rewards with 85% reinforced responses over two consecutive sessions).

Neither sex nor adult fear conditioning affected any measure of discrimination and reversal learning, so all results are reported collapsed across these two factors. Two trauma-exposed females did not acquire the discrimination in 25 sessions and were not advanced to reversal. Data were analyzed using mixed-effects analyses with phase (i.e., acquisition and reversal) as the within-subjects factor. There were no differences between groups in the total number of sessions required to complete discrimination (no shock = 5.70 ± 0.69; 15 shock = 6.82 ± 1.50) or reversal (no shock = 9.40 ± 0.98; 15 shock = 7.73 ± 1.21). Mice made more total reinforced (main effect of phase: $F_{(1,33)} = 11.62$, $P = 0.002$) and total nonreinforced (main effect of phase: $F_{(1,33)} = 42.54$, $P < 0.001$) responses during reversal but there were no effects of infant trauma on behavior (Fig. 3A,B). These results indicate that acute infant trauma does not influence acquisition of operant discrimination learning or behavioral flexibility in adulthood.

In a new cohort of mice (no shock = 16, 15 shocks = 16), novel object recognition following infant footshock was tested. In adulthood, mice were handled for 1–3 min for two consecutive days. The following day, mice were placed in 20 × 18 × 25-cm apparatus with white floors and patterned walls (Panlab) for a 10-min habituation session to the chamber. Twenty-four hours later, mice were returned to the apparatus now containing two sample objects for 10-min initial exposure to the objects (two identical small plastic caps, 0.8 cm tall with a 2.1-cm diameter) placed in the back right and left corners of the apparatus. One hour later, mice were returned to the apparatus for a 3-min session (1-h test) where one of the sample objects was replaced with a novel object (a 2.5 × 1.2 × 1.5-cm Lego tower). The object replaced was alternated for each mouse. Mice were returned to the same box 24 h later for another 3-min session (24-h test) with the opposite cap replaced with a second novel object (a 3 × 1.5-cm black binder clip). ANY-maze software recorded each session. Time spent interacting with each object was measured by two independent raters and averaged (after Bevins and Besheer 2006).

A three-way ANOVA revealed a significant main effect of object (familiar vs. novel; $F_{(1,60)} = 59.84$, $P < 0.001$). There was also a main effect of testing session (1-h vs. 24-h test; $F_{(1,60)} = 7.89$, $P = 0.007$) and an interaction of object × testing session ($F_{(1,60)} = 11.48$, $P = 0.001$) (Fig. 3C,D). Interrater reliability was confirmed using Pearson's correlation ($r = 0.942$). These results indicate that acute infant trauma does not influence hippocampal-dependent object recognition memory.

Our results demonstrate that an acute traumatic experience during infancy affects some learned behaviors during adulthood. As previously reported in rats (Quinn et al. 2014; Poulos et al. 2014), 15 footshocks on PND 17 increased adult contextual fear

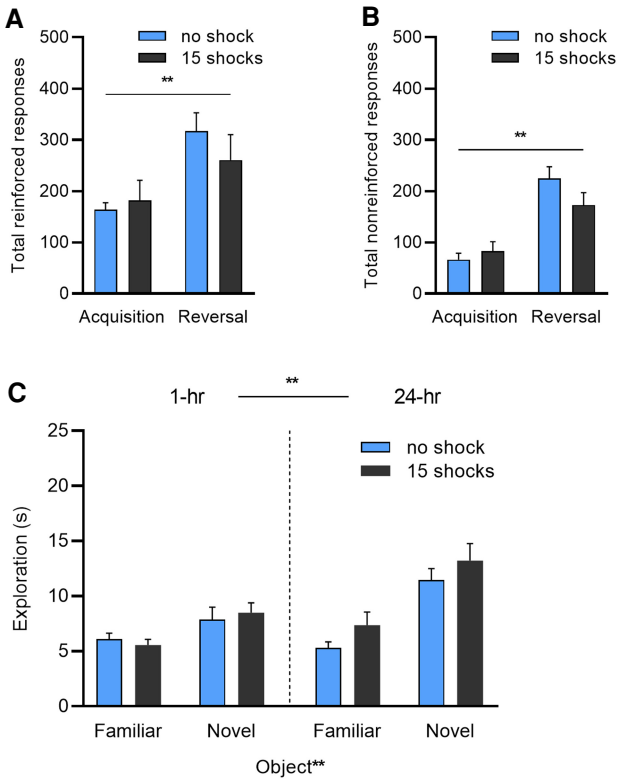

Figure 3. Acute infant trauma does not affect discrimination and reversal learning or novel object recognition. (*A*,*B*) Following infant trauma on PND 17 (no footshock, blue, or 15 footshocks, black), adult mice were trained to respond for a food pellet in an operant, spatial discrimination and reversal learning task. Following acquisition of the discrimination (left or right nose-poke hole reinforced 100% of the time) the contingencies of the responses were reversed. Mice made more total reinforced (*A*) and unreinforced (*B*) responses during reversal versus acquisition across sessions ([**] $P < 0.01$, main effect of training phase) but there were no effects of infant trauma exposure. (*C*) A separate cohort of mice exposed to infant trauma (no or 15 footshocks on PND 17) was tested for novel object recognition by assessing exploration of a novel object 1 and 24 h after exposure to the familiar object. Mice explored the novel object more ([**] $P < 0.01$, main effect of object, main effect of testing session, and interaction of object × testing session) but there were no effects of infant trauma exposure. Data are means ± SEM.

conditioning in mice. We also demonstrated for the first time that the infant SEFL protocol produces resistance to extinction (within-session and between-session) and that behavior in a discrimination and reversal learning task and a novel object recognition task are unaffected. These findings establish the use of infant footshock to study SEFL in mice and further support the use of this paradigm as a model of PTSD-like behavior.

The effects observed here differ from those commonly observed following chronic ELS manipulations such as limited nesting and bedding (Ivy et al. 2008; Molet et al. 2016) or maternal separation (Nishi et al. 2014). Chronic ELS impairs acquisition of fear conditioning in adult rodents (Kosten et al. 2006; Stevenson et al. 2009; Lesuis et al. 2019) and performance on hippocampal-dependent memory tasks (Rice et al. 2008; Naninck et al. 2015), for example. These behavioral differences suggest that acute and chronic infant stressors alter neural circuits in unique ways that are worthy of further study.

Since the tasks used here rely on distinct neural circuits, the current results provide novel insight into how acute infant trauma impacts brain function. The effects of acute ELS were restricted to fear acquisition and extinction, suggesting alterations in cortico-amygdala circuits (Tovote et al. 2015). However, preservation of novel object recognition as well as discrimination and reversal learning suggest that hippocampal and striatal circuits likely remain intact (Cohen and Stackman 2015; Izquierdo et al. 2017). These findings can guide future studies concerning the neural mechanisms of acute ELS effects on behavior.

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