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The Effect of Early-Life Stress on Memory Systems Supporting Instrumental Behavior

Tara K. Patterson,* Michelle G. Craske, and Barbara J. Knowlton

ABSTRACT: People experiencing early-life stress (ELS) exhibit increased incidence of behaviors that lead to addiction and obesity as adults. Many of these behaviors may be viewed as resulting from an overreliance on habits as opposed to goal-directed instrumental behavior. This increased habitization may result from alterations in the interactions between dorsolateral striatum-dependent and hippocampus-dependent learning systems. As an initial examination of this idea, we investigated the effect of ELS on instrumental learning and extinction. In Experiment 1, we examined the effect of ELS in two groups of people, one trained on a continuous reinforcement schedule and one trained on a partial reinforcement schedule. We found that people who experienced ELS had a diminished effect of the partial reinforcement schedule on extinction. In Experiment 2, we again manipulated reinforcement schedule and also challenged declarative memory by requiring subjects to perform a concurrent task. We found that the declarative challenge did not affect extinction responding in the non-ELS group. In a moderate-ELS group, we observed a diminished sensitivity to the reinforcement schedule during extinction only under divided attention. In the high-ELS group, we observed a reduced sensitivity to reinforcement schedule even in the absence of the declarative memory challenge, consistent with Experiment 1. Our results suggest that ELS reduces the tendency to use declarative, hippocampus-dependent memory in instrumental tasks in favor of habits. ELS may affect hippocampal development, thus altering the interaction between memory systems and potentially contributing to poor health outcomes. © 2013 Wiley Periodicals, Inc.

KEY WORDS: learning; extinction; multiple memory systems; hippocampus; dorsal striatum

INTRODUCTION

A common psychological experience beginning to garner attention is stress that occurs during development (early-life stress, ELS). In a large-scale study conducted by the Centers for Disease Control and Prevention, nearly two-thirds of survey respondents (63.9%) reported at least one adverse childhood experience, and 37.9% reported two or more adverse childhood experiences (Anda et al., 2006). Some of the most prevalent types of ELS include abuse, neglect, and household dysfunction (e.g., witnessing domestic violence).

A number of studies have linked ELS with widespread negative health outcomes, including severe obesity (Anda et al., 2006), heart disease (Dong et al., 2004), chronic obstructive pulmonary disease (Anda et al., 2008), liver disease (Dong et al., 2003), sexually transmitted disease (Hillis et al., 2000), depressive disorders (Chapman et al., 2004), and attempted suicide (Dube et al., 2001). The relationship between the breadth of childhood exposure to adversity and health in adulthood is strongly graded, with the likelihood of negative health outcomes increasing as the number of categories of exposure increases (Felitti et al., 1998).

Despite the strong links between ELS and negative health outcomes, the specific behavioral vulnerabilities that lead people who have experienced ELS to adopt health-risk behaviors are largely unknown. One candidate behavioral vulnerability is an overreliance on stimulus-response habits. Instrumental behavior can be guided by two anatomically and functionally distinct systems, a goal-directed system that learns action-outcome associations and a habit-based system that learns stimulus-response associations (for review, see Yin and Knowlton, 2006). Many negative health behaviors, especially those that contribute to addiction- and obesity-related health conditions, may be viewed as resulting from an overreliance on habits as opposed to goal-directed instrumental behavior. Habit-based responding is characterized by greater inflexibility and relies on the dorsolateral striatum (Yin et al., 2004), whereas goal-directed behavior relies on the prefrontal cortex and dorsomedial striatum (Balleine and Dickinson, 1998; Yin et al., 2005).

In the standard multiple memory systems taxonomy, memory for stimulus-response habits is a type of nondeclarative memory, and as such does not depend on the hippocampus or associated temporal cortex (Packard and Knowlton, 2002; Knowlton and Moody, 2008). Goal-directed actions, however, can be hippocampus-dependent, such as when they rely on declarative or spatial memory. For example, performance on the win-shift radial maze, a task similar to natural foraging, has been shown to be goal-directed

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and dependent on the hippocampus, whereas performance on the win-stay radial maze has been shown to be habit-based and dependent on the dorsolateral striatum (Packard et al., 1989; Sage and Knowlton, 2000).

In addition to the evidence showing that ELS in humans may result in habit-related health problems, a growing body of work indicates that stress engages the stimulus-response habit learning system relative to both goal-directed and hippocampus-dependent systems (e.g., Kim et al., 2001; Schwabe et al., 2007, 2009, 2011, 2012; Dias-Ferreira et al., 2009; Gourley et al., 2012; Schwabe and Wolf, 2009, 2013). Based on this research, we reasoned that people who have experienced ELS may be biased toward habit behavior, and may therefore show different patterns of learning in tasks requiring goal-directed action. We chose to assess the nature of instrumental learning by evaluating extinction after training with continuous or partial reinforcement. A well-known finding in instrumental learning is that a behavior trained on a partial reinforcement schedule will persist longer in extinction than a behavior trained on a continuous reinforcement schedule, despite taking longer to acquire. This partial reinforcement extinction effect (PREE) has been demonstrated repeatedly in both humans and non-human animals (for reviews, see Jenkins and Stanley, 1950; Lewis, 1960). There have been two leading theoretical accounts of the PREE. By one view (frustration theory; Amsel, 1958, 1967), the absence of reward on some trials increases frustration during learning under partial reinforcement. These frustration cues become associated with reward during training. Thus, under extinction, when there is also frustration, the frustration cues impair extinction of the response because they have become a signal for reward. By another view (sequential theory; Capaldi, 1966, 1967), the PREE is based on memory for events during training. If nonreinforced trials are held in memory, these will become conditioned to the reinforcer during training. Thus, during extinction, when all trials are nonreinforced, the sequence of trials resembles the learner's memory for the training session, where there were sequences of nonreinforced trials before reward trials. Because of the similarity between the extinction trials and the memory for the training trials, responding continues for a while at a similar rate to training. In contrast, if each trial was reinforced during training, extinction trials are very different than memory for the training trials, and response rates decrease. Thus, the important feature of sequential theory is the reliance on memory for the recent sequence of rewards and nonrewards, rather than the emotional component of nonrewards.

In non-human animals, the PREE is attenuated or abolished by lesions to the septum (Henke, 1974), fornix-fimbria (Feldon et al., 1985), and hippocampal formation (Rawlins et al., 1980; Jarrard et al., 1986). Thus, it appears that the hippocampal system plays a critical role in mediating the relative effects of partial reinforcement training on extinction behavior. In these experiments, hippocampal system lesions were found to increase persistence of responding in extinction after continuous reinforcement, decrease persistence of responding in extinction after partial reinforcement, or both. Other regions shown to be critical for the PREE include the nucleus accumbens (Tai et al., 1991) and medial prefrontal cortex (Yee, 2000).

Henke (1974) and Amsel (1986) have offered frustration theory-based accounts of the effects of hippocampal system lesions on the PREE. An alternative explanation consistent with both a multiple memory systems framework as well as Capaldi's (1966, 1967) sequential theory is that hippocampal lesions prevent the use of episodic memory for the pattern of rewards and nonrewards experienced during training, but do not prevent the use of dorsolateral striatum-dependent habit memory. Thus, animals lacking an intact hippocampal system would still be able to learn the rewarded response by forming stimulus-response associations, and their behavior in extinction would be a reflection of the strength of these associations. Animals with an intact hippocampus, on the other hand, can behave in a goal-directed manner that reflects their reinforcement history. In the case of continuous reinforcement, memory for reinforcement history accelerates extinction relative to the level of responding supported by habit strength, whereas in the case of partial reinforcement, memory for reinforcement history increases persistence relative to the level supported by habit. Thus, in both cases, declarative memory for the sequence of rewards and nonrewards experienced during training pushes behavior away from the level of persistence supported by habit strength, resulting in a decreased PREE. This view is also consistent with the effects of medial prefrontal and nucleus accumbens lesions on the PREE given the roles of these two regions in representing outcome value, which is an important component of goal-directed behavior (Schultz et al., 1997; Balleine and Dickinson, 1998; Killcross and Coutureau, 2003).

Based on this idea, we designed two experiments using the PREE as a way to probe the extent to which episodic memory may be contributing to the instrumental behavior of adults who have a history of ELS. We hypothesized that people who experience ELS would show an overreliance on habit responding and reduced reliance on hippocampus-dependent memory, which would be expressed as a reduction in the PREE. In Experiment 1, we measured instrumental behavior in participants who were trained with either continuous or partial reinforcement, and we classified participants into two groups based on their responses to a questionnaire that measures experience with ELS. In Experiment 2, we sought to replicate the findings of Experiment 1 in a larger sample to investigate dosage effects of ELS on the PREE. In this experiment we included a declarative memory challenge condition in which participants performed a concurrent tone-counting task during acquisition and extinction of the instrumental response. Past research has shown that hippocampus-dependent declarative learning is impaired by divided attention, whereas dorsolateral striatum-dependent habit learning is not (Foerde et al., 2006, 2007). We were thus able to use the divided attention condition as a way to challenge declarative memory to examine whether this challenge led to a greater reliance on habitual performance in individuals with ELS.

EXPERIMENT 1

Materials and Methods

Participants

Study participants were recruited from the undergraduate student population at the University of California, Los Angeles. Study procedures were approved by the Institutional Review Board of the University of California Los Angeles, and all participants provided written record of informed consent. Participants were compensated for their time at the rate of $10.00 per hour or one credit per hour toward partial fulfillment of course requirements. Participants were also compensated $.25 for each correct response they made in the instrumental reward-learning task. Participants in the continuous reinforcement condition were able to earn a $5.00 bonus and participants in the partial reinforcement condition were able to earn a $2.50 bonus.

A total of 79 participants were recruited. Six provided partial data and were not included in the analysis, yielding a sample size of 73 (59 women, 14 men, M_{age} = 19.82 yr, SD_{age} = 1.37 yr, age range: 18–23 yr).

Design and procedure

The instrumental reward-learning task was adapted from Vogel-Sprott (1967). Participants were instructed that their task was to learn which four-button sequence(s) received a $.25 reward. Participants were told that they could choose to press the four buttons in any order, provided that no button was pressed twice within the same response. The fifth sequence the participant entered was rewarded, and each subsequent entry of this sequence was scored as a correct response. Although the reward was only administered for one particular sequence, participants were not informed of this. Participants were randomly assigned to one of two between-subjects experimental conditions, continuous reinforcement or partial reinforcement.

In the continuous reinforcement condition, participants received acquisition training on a continuous reinforcement schedule, receiving a $.25 reward for each correct response. In the partial reinforcement condition, participants received acquisition training on a partial reinforcement schedule, receiving a $.25 reward for 50% of the trials on which they entered the correct response. The reward sequence for participants under partial reinforcement was constrained such that participants received no more than two rewards consecutively. After 20 correct responses had been obtained, participants completed 40 trials of extinction during which no rewards were given.

Stimulus appearance and trial timing was the same for both acquisition and extinction. Each trial of the instrumental learning task began with a black fixation cross presented on a white background for 4 s. Next, participants were prompted to enter a four-button response. Following the fourth button press, participants were asked to rate on a scale of one to five their expectation that their last response would receive a reward (1 = low expectation, 5 = high expectation). After a 5 s delay, participants viewed a 2 s feedback stimulus indicating reward or no reward. Participants were allowed as much time as they needed to enter the four-button response and the expectancy judgment. The instrumental learning task was completed on a 2.66 GHz Macintosh computer in a private testing booth. Button press responses and expectancy ratings were made using the computer keyboard. Responses were recorded with E-Prime Standard (Version 2.0) experimental software.

Questionnaires were used to assess anxiety, depression, personality factors, and ELS. State and trait anxiety were measured using the 40-item State-Trait Anxiety Inventory (STAI; Spielberger, 1983). Participants completed the state anxiety form twice during the experimental session, first immediately after informed consent, and again after the instrumental learning task. All other questionnaires were completed after the instrumental learning task. The 14-item Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) was used to measure anxiety and depression symptoms experienced over the past week. Personality was assessed with the Big Five Inventory (BFI; John et al., 1991, 2008), a 44-item measure that yields subscale scores of extraversion, agreeableness, conscientiousness, neuroticism, and openness.

Eighteen items from the Adverse Childhood Experiences Questionnaire (ACEQ; Felitti et al., 1998; Anda et al., 2006) assessed exposure to stress during the first 18 yr of life. The ACEQ was scored 0–8 representing the number of categories of stress experienced (Anda et al., 2006). The eight exposure categories were: emotional abuse, physical abuse, sexual abuse, witnessing domestic violence, parental separation or divorce, household substance abuse, household mental illness, and having a criminal household member. Participants were blocked into two groups, those scoring 0 (non-ELS group) and those scoring 1 or higher (ELS group). The distribution of the ELS groups over the two reinforcement conditions was as follows: non-ELS continuous reinforcement, $n = 21$; non-ELS partial reinforcement, $n = 16$; ELS continuous reinforcement, $n = 16$; ELS partial reinforcement, $n = 20$.

Performance data and expectancy data were computed separately for acquisition and extinction and were submitted to 2 (schedule: continuous, partial) $\times$ 2 (stress: non-ELS, ELS) ANOVA. We also conducted planned comparisons to test the hypothesis that individuals with ELS would show a reduced PREE. A significance level of 0.05 was used for all statistical tests.

Results

Sample characteristics

The prevalence of exposure to ELS in the sample was as follows: emotional abuse, 16.4%; physical abuse, 2.7%; sexual abuse, 11.0%; witnessing domestic violence, 4.1%; parental separation or divorce, 15.1%; household substance abuse, 11.0%; household mental illness, 20.5%; having a criminal household member, 1.4%. The percentages of the sample exposed to 0, 1, 2, 3, 4, and 5 categories of ELS were 50.7%, 28.8%, 13.7%, 2.7%, 2.7%, and 1.4%, respectively; no participants reported exposure to $\geq$6 categories. The ELS group did not differ

TABLE 1.

Sample Characteristics

	Experiment 1		Experiment 2		
	Non-ELS	ELS	Non-ELS	Moderate-ELS	High-ELS
STAI					
State anxiety (pre)	31.95 (8.27)	35.14 (7.48)	33.84 (9.30)	34.65 (10.35)	34.41 (8.13)
State anxiety (post)	37.84 (11.51)	37.42 (9.78)	38.77 (11.41)	37.69 (11.39)	38.71 (10.67)
Trait anxiety	39.39 (7.20)	40.64 (9.30)	40.76 (9.98)	41.79 (11.58)	45.78 (12.84)
HADS					
Anxiety	6.76 (3.70)	7.25 (3.04)	7.22 (3.74)	7.82 (4.31)	9.56 (4.27)
Depression	2.78 (2.26)	3.39 (2.95)	3.67 (3.03)	3.77 (3.07)	4.54 (3.80)
BFI					
Extraversion	3.22 (0.63)	3.23 (0.85)	3.18 (0.86)	3.37 (0.88)	3.20 (0.91)
Agreeableness	3.84 (0.56)	3.81 (0.64)	3.92 (0.60)	3.75 (0.65)	3.74 (0.78)
Conscientiousness	3.75 (0.53)	3.75 (0.64)	3.66 (0.69)	3.70 (0.71)	3.39 (0.80)
Neuroticism	2.81 (0.67)	3.05 (0.76)	2.82 (0.83)	2.85 (0.91)	3.20 (0.95)
Openness	3.46 (0.65)	3.58 (0.63)	3.57 (0.63)	3.76 (0.59)	3.62 (0.68)
ACEQ	0	1.67 (1.01)	0	1.41 (0.50)	3.68 (0.99)

Mean (SD) scores on questionnaire measures for participants grouped by stress exposure. ELS, early-life stress; STAI, State Trait Anxiety Inventory (Spielberger, 1983); HADS, Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983); BFI, Big Five Inventory (John et al., 1991, 2008); ACEQ, Adverse Childhood Experiences Quesionnaire (Felitti et al., 1998; Anda et al., 2006).

significantly from the non-ELS group on any subscales of the STAI, HADS, or BFI, smallest $P > 0.05$ (see Table 1).

Acquisition

The number of trials required by each group to obtain the criterion of 20 correct responses is shown in Figure 1A. Consistent with previous findings, we observed a significant main effect of reinforcement schedule during acquisition, with slower learning in the partial reinforcement group than the continuous reinforcement group, $F(1, 69) = 21.98$, $P < 0.001$. The main effect of ELS was marginal, $F(1, 69) = 3.97$, $P = 0.050$. The direction of this trend was toward a greater number of acquisition trials required by the ELS group than the non-ELS group. The interaction was not significant, $F(1, 69) = 0.38$, $P = 0.542$.

The expectation of reward during acquisition is shown in Figure 1B. Participants assigned to the continuous reinforcement schedule had a higher expectation of reward compared with participants learning under partial reinforcement, $F(1, 69) = 32.90$, $P < 0.001$. The main effect of ELS was also significant, $F(1, 69) = 4.67$, $P = 0.034$, such that the expectation of reward was higher in the non-ELS group than in the ELS group. The interaction was not significant, $F(1, 69) = 0.93$, $P = 0.339$.

Extinction

The extinction behavior of each group in Experiment 1 is shown in Figure 2A (extinction means) and Supporting Information Figure S1 (extinction time courses). We observed a significant main effect of reinforcement schedule on the number of correct (previously rewarded) responses made in extinction, $F(1, 69) = 97.63$, $P < 0.001$. The number of correct responses was significantly higher after partial reinforcement compared with continuous reinforcement, replicating the PREE found in previous studies of reward schedule effects in extinction. The main effect of ELS was not significant, $F(1, 69) = 1.83$, $P = 0.180$, and the interaction between ELS and schedule was not significant, $F(1, 69) = 2.67$, $P = 0.107$. Specific planned hypothesis tests revealed that in the continuous reinforcement condition, there was no significant difference between the ELS group and the non-ELS group, $F(1, 69) = 0.04$, $P = 0.844$. In the partial reinforcement condition, however, the effect of ELS was significant, $F(1, 69) = 4.41$, $P = 0.039$, such that the number of correct responses in extinction was significantly lower for participants who reported ELS compared with non-ELS participants.

The expectation of reward during extinction is shown in Figure 2B. In contrast to the pattern found during acquisition, participants trained on a partial reinforcement schedule had a higher expectation of reward, $F(1, 69) = 5.69$, $P = 0.020$. The main effect of ELS was also significant, $F(1, 69) = 5.38$, $P = 0.023$, such that the expectation of reward was higher in the non-ELS group than in the ELS group. The interaction effect was not significant, $F(1, 69) = 0.01$, $P = 0.905$.

EXPERIMENT 2

In Experiment 1, we found support for the hypothesis that the ELS group had a diminished effect of the partial reinforcement schedule on extinction, consistent with the view that

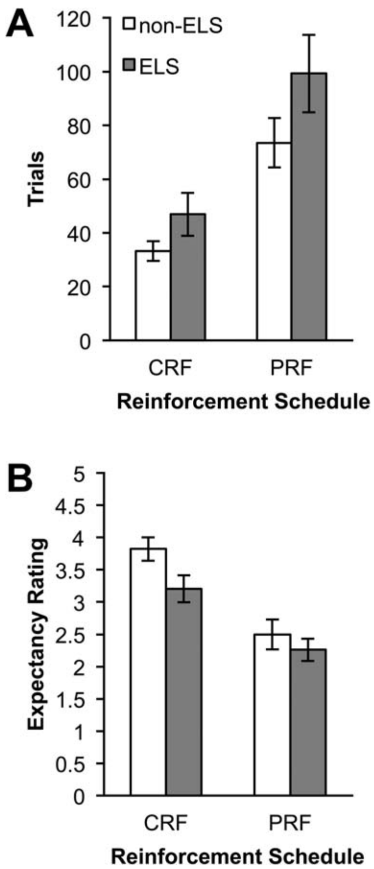

FIGURE 1. Experiment 1: Effects of early-life stress (ELS) and reinforcement schedule on acquisition behavior. Mean (±SEM) number of trials required to reach the criterion of 20 correct responses (A) and expectation of reward given for each trial on a scale of 1–5 (B). CRF, continuous reinforcement (100% of correct responses rewarded); PRF, partial reinforcement (50% of correct responses rewarded).

instrumental learning in this group relied less on goal-directed declarative learning and more on habit learning. In this experiment, participants reporting at least one significant stressor in early life were considered to be in the ELS group. Because the amount of ELS has been shown to be related to the likelihood of negative health behaviors (Felitti et al., 1998), it is possible that there is a "dosage effect" with increasing tendency for habitual responding with greater exposure to ELS. In Experiment 2, we recruited a larger sample of participants to be able to stratify participants into high-, moderate-, and non-ELS participants.

In Experiment 2, we also added a condition in which subjects performed the instrumental task under distraction. This declarative memory challenge condition provided a more sensitive test of the tendency for reliance on habit learning in our task.

Materials and Methods

Participants

In Experiment 2, we recruited from the same undergraduate population as Experiment 1, but advertising and screening procedures were implemented to over-sample for ELS in order to gain the statistical power to investigate dosage effects. Study procedures were approved by the Institutional Review Board of the University of California Los Angeles, and all participants provided written record of informed consent. Compensation procedures were the same as in Experiment 1.

A total of 242 participants were recruited. Twenty-three provided partial data and were not included in the analysis. Of the 219 remaining participants, five were excluded for failure to comply with the tone-counting task instructions, and two were excluded for poor performance on the tone-counting task. This yielded a final sample size of 212 (162 women, 50 men, M_{age} = 20.21 yr, SD_{age} = 2.29 yr, age range: 18–39 yr).

Design and procedure

Participants in Experiment 2 performed the instrumental reward-learning task under either continuous or partial reinforcement as described for Experiment 1. The trial structure differed from that used in Experiment 1 in the following ways: the delay period preceding feedback was shortened from 5 s to 2 s, the feedback presentation period was shortened from 2 s

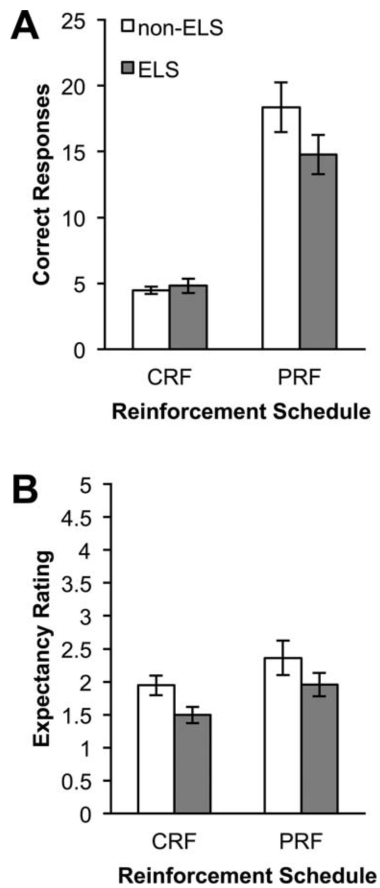

FIGURE 2. Experiment 1: Effects of early-life stress (ELS) and reinforcement schedule on extinction behavior. Mean (±SEM) number of correct responses (A) and expectation of reward given for each trial on a scale of 1–5 (B). CRF, continuous reinforcement (100% of correct responses rewarded); PRF, partial reinforcement (50% of correct responses rewarded).

to 1 s, and the expectancy ratings were eliminated. These changes served to shorten the procedure to reduce fatigue.

Half of the participants in Experiment 2 were assigned to a declarative memory challenge condition; these participants were required to perform a concurrent tone-counting task during acquisition and extinction of the instrumental reward-learning task. Participants assigned to perform the concurrent tone-counting task heard high- (1,000 Hz) and low- (500 Hz) pitched tones during the fixation period of each instrumental learning trial. They were instructed to keep a running count of the high-pitched tones and ignore the low-pitched tones. After every 10 trials, the dual-task participants were prompted to enter the number of high-pitched tones they had heard.

The questionnaire measures were the same as in Experiment 1. To investigate the effects of ELS severity in this larger sample, participants were blocked into three groups based on their responses to the ACEQ. Participants who scored 0, 1–2, and 3 or higher were coded as non-ELS, moderate-ELS, and high-ELS, respectively. The distribution of the ELS groups over the four experimental conditions was as follows: non-ELS continuous reinforcement single-task, $n = 24$; non-ELS continuous reinforcement dual-task, $n = 21$; non-ELS partial reinforcement single-task, $n = 22$; non-ELS partial reinforcement dual-task, $n = 19$; moderate-ELS continuous reinforcement single-task, $n = 21$; moderate-ELS continuous reinforcement dual-task, $n = 23$; moderate-ELS partial reinforcement single-task, $n = 22$; moderate-ELS partial reinforcement dual-task, $n = 19$; high-ELS continuous reinforcement single-task, $n = 10$; high-ELS continuous reinforcement dual-task, $n = 10$; high-ELS partial reinforcement single-task, $n = 10$; high-ELS partial reinforcement dual-task, $n = 11$.

Performance data were computed separately for acquisition and extinction and were submitted to 2 (task: single-task, dual-task) × 2 (schedule: continuous, partial) × 3 (stress: non-ELS, moderate-ELS, high-ELS) ANOVA. Planned comparisons were conducted to investigate the hypothesis that the high-ELS group would show reduced PREE, and the moderate-ELS group would show reduced PREE under the declarative memory challenge. A significance level of 0.05 was used for all statistical tests.

Results

Sample characteristics

Recruitment efforts to increase the proportion of people reporting ELS in the second sample were successful. The prevalence of exposure to ELS was as follows: emotional abuse, 22.2%; physical abuse, 4.2%; sexual abuse, 11.3%; witnessing domestic violence, 14.2%; parental separation or divorce, 27.8%; household substance abuse, 18.4%; household mental illness, 26.4%; having a criminal household member, 3.3%. The percentages of the sample exposed to 0, 1, 2, 3, 4, 5, and 6 categories of ELS were 40.6%, 23.6%, 16.5%, 11.3%, 4.7%, 1.4%, and 1.9%, respectively; no participants reported exposure to ≥7 categories. Scores for each ELS group on the questionnaire measures are shown in Table 1. There was a significant effect of ELS on the HADS anxiety subscale, $F(2, 209) = 4.61$, $P = 0.011$. Pairwise comparisons indicated that this effect was driven by higher anxiety in the high-ELS group compared to the non-ELS group, $F(1, 209) = 9.14$, $P = 0.003$. The moderate-ELS group did not differ from the non-ELS group, $F(1, 209) = 0.93$, $P = 0.335$. Inclusion of this factor as a covariate did not change the observed pattern of results. There was no significant effect of ELS on any of the other questionnaire variables (STAI, BFI, depression), $P > 0.05$.

For participants assigned to the declarative memory challenge condition, performance on the secondary task was assessed by calculating the absolute difference between the reported number of counted tones and the target number of tones divided by the target number and multiplied by 100. The average deviation score was low ($M = 11.42$, SD = 9.66). The effect of ELS on tone-counting performance was not significant, $F(2, 100) = 2.18$, $P = 0.118$.

Acquisition

Acquisition data from Experiment 2 are shown in Figure 3. Consistent with Experiment 1 and previous studies, we

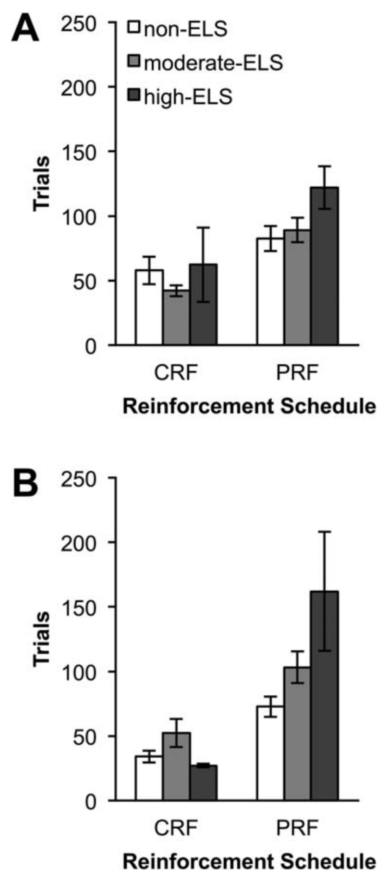

FIGURE 3. Experiment 2: Effects of early-life stress (ELS), reinforcement schedule, and distraction on acquisition behavior. Mean (±SEM) number of trials required to reach the criterion of 20 correct responses for participants in the single-task condition (A) and the dual-task condition (B). CRF, continuous reinforcement (100% of correct responses rewarded); PRF, partial reinforcement (50% of correct responses rewarded).

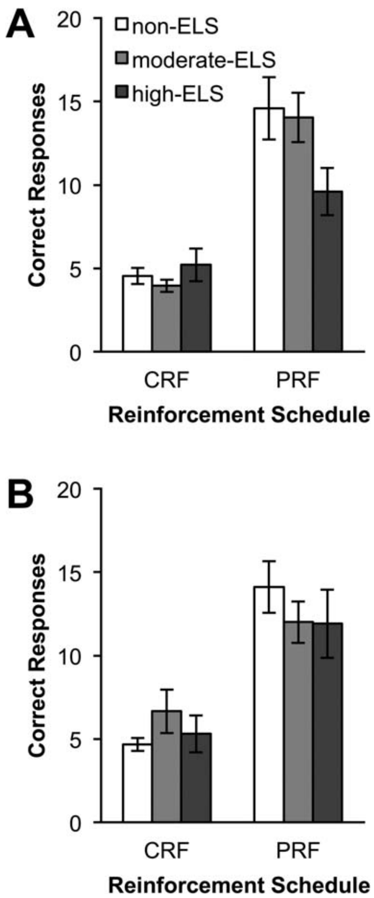

FIGURE 4. Experiment 2: Effects of early-life stress (ELS), reinforcement schedule, and distraction on extinction behavior. Mean (±SEM) number of correct responses for participants in the single-task condition (A) and the dual-task condition (B). CRF, continuous reinforcement (100% of correct responses rewarded); PRF, partial reinforcement (50% of correct responses rewarded).

observed slower acquisition in participants who received partial reinforcement compared to participants who received continuous reinforcement, $F(1, 200) = 52.47$, $P < 0.001$. There was also a significant effect of ELS on the number of acquisition trials, $F(2, 200) = 4.40$, $P = 0.014$, and a significant interaction between reinforcement schedule and ELS, $F(2, 200) = 4.77$, $P = 0.009$. The effect of ELS on acquisition was highly significant for participants trained under partial reinforcement, $F(2, 200) = 9.18$, $P < 0.001$, but was not significant for participants trained under continuous reinforcement, $F(2, 200) = 0.01$, $P = 0.986$. In the partial reinforcement condition, high-ELS participants required significantly more acquisition trials than both non-ELS participants, $F(1, 200) = 18.28$, $P < 0.001$, and moderate-ELS participants, $F(1, 200) = 9.24$, $P = 0.003$. The difference between non-ELS participants and moderate-ELS participants under partial reinforcement was not significant, $F(1, 200) = 2.25$, $P = 0.135$.

The main effect of the secondary task was not significant, and there were no significant interactions between task and the other factors, smallest $P > 0.05$.

Extinction

Extinction data from Experiment 2 are shown in Figure 4 (extinction means) and Supporting Information Figure S2 (extinction time courses). Overall, there was a significant main effect of reinforcement schedule on extinction responding, with higher responding after partial reinforcement, $F(1, 200) = 92.43$, $P < 0.001$. This replicates the PREE observed in Experiment 1 and previous studies. We did not observe main effects of ELS, $F(2, 200) = 1.03$, $P = 0.358$, or of task, $F(1, 200) = 0.32$, $P = 0.572$. The three-way interaction between schedule, ELS, and task was also not significant, $F(2, 200) = 1.59$, $P = 0.207$. Consistent with the results of Experiment 1, among participants in the single-task condition we observed a significant effect of ELS on responding after partial reinforcement, $F(2, 200) = 3.10$, $P = 0.047$. Specific hypothesis testing revealed that this effect was due to reduced persistence in the high-ELS single-task group compared with both the non-ELS single-task group, $F(1, 200) = 5.76$, $P = 0.017$, and the moderate-ELS single-task group, $F(1, 200) = 4.57$, $P = 0.034$. There was not a significant difference between the non-ELS single-task group and the moderate-ELS single-task group, $F(1, 200) = 0.11$, $P = 0.740$.

We next investigated the effects of the declarative challenge condition. The declarative challenge did not affect the size of the PREE in the non-ELS group, shown by a non-significant interaction between task and schedule, $F(1, 200) = 0.07$, $P = 0.796$. In the high-ELS group, the interaction between task and schedule was also non-significant, $F(1, 200) = 0.42$, $P = 0.518$. This indicates that in the high-ELS group, which had diminished extinction responding even in the absence of a secondary task, there was no additional impact of declarative challenge. In the moderate-ELS group, however, we observed a significant task by schedule interaction, $F(1, 200) = 4.00$, $P = 0.047$. This interaction was characterized by a numerical increase in persistence after continuous reinforcement, $F(1, 200) = 2.69$, $P = 0.103$, and a numerical decrease in persistence after partial reinforcement, $F(1, 200) = 1.43$, $P = 0.233$, in response to the declarative challenge.

DISCUSSION

With this pair of experiments, we demonstrate that a different pattern of instrumental responding is associated with a history of ELS. Using a classic reward-learning paradigm, we showed that people who reported ELS exhibited a slower rate of learning and decreased persistence in extinction after partial reinforcement. It is not the case, however, that extinction responding in ELS participants was lower overall; after continuous reinforcement, the ELS participants maintained response levels that were equivalent to or numerically higher than their non-ELS counterparts. Interestingly, this maintained responding occurred in the presence of significantly lower expectation of reward. Furthermore, when we gave learners a concurrent declarative memory challenge, we found that participants who reported moderate levels of ELS showed diminished sensitivity in extinction to the reinforcement schedule they had experienced during acquisition. Under single-task conditions, these participants performed similarly to non-ELS participants, but under dual-task conditions, their behavior more closely resembled the behavior of the high-ELS group, with increased persistence after continuous reinforcement and decreased persistence after partial reinforcement. These results emerged using planned comparisons based on our hypotheses. However, the effects of ELS were fairly modest, which may have been due to the nature of our sample. As evidenced by their enrollment in university, individuals experiencing ELS in this group may have been more resilient than individuals experiencing ELS in general. Nevertheless, even in this high functioning sample, we found data consistent with our hypothesized effects of ELS on instrumental learning. Future work with more widely representative samples would be important to determine the generalizability of these effects.

We propose that the observed effects of ELS can be explained by differential use of multiple memory systems in this population. Capaldi's (1966, 1967) sequential theory and lesion studies in rodents (Henke, 1974; Rawlins et al., 1980; Feldon et al., 1985; Jarrard et al., 1986) support the idea that the PREE relies on hippocampus-dependent learning. An overreliance on the habit learning system instead of hippocampus-dependent, goal-directed responding may result in slower acquisition, consistent with the idea that habit system representations are built up slowly across many trials (Knowlton and Moody, 2008). In extinction, weaker episodic memory for the pattern of rewards and nonrewards experienced during training would in turn result in behavior driven more by habit strength, which falls between the levels of responding produced by strong episodic memory of continuous reinforcement and strong episodic memory of partial reinforcement. Our data suggest that high levels of ELS, or moderate levels of ELS in combination with declarative challenge, produce these predicted impairments. The observed dissociation between expectation ratings and behavior, characterized by persistent responding in ELS participants despite relatively low expectation of reward, could also be a mark of increased habitization in this population.

Mounting evidence suggests that acute and chronic stress lead to increased use of the habit learning system, both in terms of behavior and neural substrates, relative to goal-directed and hippocampus-dependent systems (e.g., Kim et al., 2001; Schwabe et al., 2007, 2009, 2011; Dias-Ferreira et al., 2009; Gourley et al., 2012; Schwabe and Wolf, 2009, 2013). Also, there is preliminary evidence that stress during development can have lasting effects on the relative use of these multiple memory systems later in life (Grissom et al., 2012; Schwabe et al., 2012). This study adds to the body of evidence in support of this claim. It is also, to our knowledge, the first investigation into the effects of postnatal developmental stress on interactions between multiple memory systems in humans. Given the sensitivity of the hippocampal system to stress (de Kloet et al., 2005; Pittenger and Duman, 2008; Lupien et al., 2009), it is possible that ELS affects hippocampal development, setting the stage for a compensatory dominance of habit responding.

Many previous investigations have used pharmacological manipulations to assess the effects of stress on the use of multiple memory systems (e.g., Schwabe et al., 2009; Gourley et al., 2012). A benefit of this technique is that it allows precise control over the timing of the stress, and can allow for isolation of the specific neural structures that mediate the shift toward habit responding. Studies that investigate non-pharmacologically induced stress, on the other hand, provide insight about the effects of stressors that occur at physiological levels, and thus have the potential for greater ecological validity. Similarly, much of the research conducted to date has been done with non-human animals (e.g., Kim et al., 2001; Dias-Ferreira et al., 2009; Grissom et al., 2012), allowing for high levels of induced stress over short periods of time. We would argue that although these types of experiments have provided information about what is possible, they offer less in terms of what is typical. Experiments such as ours help generate a more complete picture of stress effects in the general population.

The results of the current study also offer a potential explanation for the negative health outcomes observed in people who have experienced ELS. Future research should address this potential link directly, by measuring health behavior. Another direction of future research is the investigation of factors that mediate and moderate the effects of ELS on engagement of habit responding. For example, higher anxiety has been associated with ELS previously (Stein et al., 1996; Anda et al., 2006), and this increased level of anxiety was also present in high-ELS participants in this study. Inclusion of this factor as a covariate did not affect the pattern of results, indicating that ELS contributed to the measured behaviors over and above any effect of anxiety. However, it is quite likely that anxiety may be a partial mediator of the effects of ELS on the overreliance on habit, and reducing anxiety may help attenuate this effect.

This study has several limitations. First, there were differences in acquisition rate of the rewarded response in ELS and non-ELS groups. Although both groups were trained until they received the same number of rewards, it is possible that the ELS participants learned the response less well, and as a result forgot it more quickly. This may not have been apparent in the continuous reinforcement condition because extinction was rapid for both groups. An interesting replication test would involve overtraining prior to extinction. Second, the changes we implemented in Experiment 2 to reduce participant fatigue may have influenced our results, limiting comparison across the two experiments. Another limitation of the current study is the use of behavioral measures to test hypotheses about underlying neural processes. Therefore, an important next step for this area of research is the incorporation of neuroimaging techniques to assess the proposed effects of ELS on interactions between multiple memory systems. Finally, it will be important for future studies to validate our procedure for assessing the goal-directedness of instrumental behavior by measuring sensitivity to outcome devaluation or contingency degradation. These procedures, which are the standard methods employed in research on habit behavior in non-human animals, are not well-suited for work with human subjects. Therefore, the proposed technique of using sensitivity to reinforcement history as a way to probe whether an instrumental behavior is goal-directed or habit-based may be a useful alternative to traditional methods, which would aid in the advancement of translational research.

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