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Effects of Early-Life Stress on Actions, Habits, and the Neural Systems Supporting Instrumental Behavior

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Effects of Early-Life Stress on Actions, Habits, and the Neural Systems Supporting Instrumental Behavior

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Psychology

by

Tara Kathleen Patterson

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ABSTRACT OF THE DISSERTATION

Effects of Early-Life Stress on Actions, Habits,
and the Neural Systems Supporting Instrumental Behavior

by

Tara Kathleen Patterson
Doctor of Philosophy in Psychology
University of California, Los Angeles, 2017
Professor Barbara Knowlton, Chair

Factors contributing to the formation of habits, defined as the stimulus-response associations that form the basis of much human and animal behavior, are not well understood, and although habits are believed to underlie many negative health behaviors such as addictions, the extent to which findings from animal research on habits apply in the human is largely unknown. In Study 1 (Chapter 2), we conducted two experiments on appetitive habit formation in adults with a history of early-life stress. Using the size of the partial reinforcement extinction effect as a measure of goal-directed versus habit behavior, we found evidence of increased habit behavior in people who reported a history of early-life stress, and this effect appeared to be enhanced by the presence of distraction. In Study 2 (Chapter 3), we conducted two experiments on avoidance habit formation in this population. People with a history of early-life stress exhibited enhanced avoidance habits as measured by persistence of learned behaviors after outcome devaluation.

Finally, in Study 3 (Chapter 4), we conducted a meta-analysis of fMRI studies on human habit responding to assess the contributions of striatal subregions to habit behavior. We found that activation patterns varied based on the task that was used (probabilistic classification, maze navigation, outcome devaluation, sequential decision, or motor sequence learning), with differences observed along both the anterior-posterior and medial-lateral axes. Chapter 5 summarizes the findings and makes suggestions for future research.

The dissertation of Tara Kathleen Patterson is approved.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Acknowledgments

Chapter Two was published as "The effect of early-life stress on memory systems supporting instrumental behavior," Tara K. Patterson, Michelle G. Craske, and Barbara J. Knowlton, Hippocampus 23:1025-1034, Copyright © 2013, Wiley Periodicals, Inc.

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PUBLICATIONS

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CHAPTER 1

General Introduction and Overview of Studies

A major accomplishment of memory research over the past 50 years has been establishing the existence of multiple memory systems in the brain, which specialize in learning different types of information and have distinct neural substrates that support their correct function. Some of the earliest evidence for the multiple memory systems hypothesis came from observations that patients with hippocampal lesions such as H.M. retained the ability to learn some types of new information in spite of profound deficits in the functioning of the declarative memory system (Milner et al., 1998). One type of memory that is spared by this condition is habit memory, which is defined as stimulus-response associations that are formed when the learner receives a desired outcome or avoids an undesired outcome (Knowlton, 2002; Packard, 2009; Packard and Knowlton, 2002).

Early in learning, behavior is "goal-directed" and is guided primarily by associations between responses and outcomes, but as habits develop, behavior comes to be guided primarily by associations between stimuli and responses (Dickinson, 1985). After a habit has formed, it is elicited automatically by the presence of the stimulus, and performance of the response behavior persists even when outcomes that previously had motivational value do not have value any longer. For example, an animal that has a habitual association between a lever and lever pressing behavior may continue to perform the lever pressing behavior when the lever is present even after the food reward associated with the lever pressing behavior has been devalued by taste aversion conditioning or sensory-specific satiety (Adams, 1982; Colwill and Rescorla, 1985).

Lesion studies in non-human animals have shown that habits and goal-directed behaviors are supported by distinct neural structures: habit behavior relies on the dorsolateral striatum, while goal-directed behavior relies on the dorsomedial striatum and prefrontal cortex (Balleine and Dickinson, 1998; Yin and Knowlton, 2004; Yin et al., 2004; Yin et al., 2005). Based on these findings, Yin and Knowlton (2006) suggested that the formation of habits corresponds to a shift in the control of behavior from a "sensorimotor" corticostriatal loop that contains the dorsolateral striatum to an "associative" corticostriatal loop that contains the dorsomedial striatum. Although this explanation fits well with the findings from non-human animals, the extent to which this occurs in the human brain has not been determined. Indeed, only within the past decade has there arisen evidence that humans form stimulus-response associations that are insensitive to the devaluation manipulations that have long been understood in rodents (Tricomi et al., 2009).

One of the latest developments in this area of research has been the observation that stress increases habitual responding. This was first demonstrated in rodents in a study conducted by Kim et al. (2001), who showed that animals exposed to acute stress had impaired spatial memory and enhanced stimulus-response memory compared to non-stressed controls. In the nearly two decades since this landmark study, similar effects have been demonstrated in humans (Schwabe et al., 2007), and chronic stress has been shown to induce greater habit responding even when animals are tested after a stress-free delay (Schwabe et al., 2008). The persistence of such effects through a period of recovery raises important questions about how long the effects of stress on habit behavior last. A study conducted with adult humans under stress lasting on the order of months found that the neural and behavioral changes to the habit memory system reversed when the stress was removed (Soares et al., 2012), but studies in which stress occurs

prenatally or soon after birth have shown effects on habit memory persisting into adolescence and adulthood (Grissom et al., 2012; Schwabe et al., 2012). These data point toward the possibility that stress occurring during a sensitive period of development (early-life stress, ELS) may alter neural trajectories, creating a system that is inclined toward greater habit responding throughout the life of the organism.

The focus of this dissertation was to investigate the habit memory system in humans, an area that has been greatly understudied relative to what we know about habit behavior in rodents and to the potential implications of such research for issues of human health and happiness. In Study 1 (Chapter 2), we conducted two experiments on appetitive habit formation in adults with a history of ELS. In Study 2 (Chapter 3), we conducted two experiments investigating the effects of ELS on formation of avoidance habits. Finally, in Study 3 (Chapter 4), we conducted a meta-analysis of fMRI studies on human habit responding to assess how the activation of striatal subregions varies across different methods for studying habits. There exists some controversy in the literature with regard to the roles of specific striatal subregions in habit behavior, and a well-defined region of interest would be useful for future research. Furthermore, identifying specific regions of the human brain that support habit behavior is an important intermediate step toward investigating the functioning of these regions in people with a history of ELS. Chapter 5 summarizes the findings and makes suggestions for future research.

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CHAPTER 2

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

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 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) × 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 ≥ 6 categories.

The ELS group did not differ significantly from the non-ELS group on any subscales of the STAI, HADS, or BFI, smallest $p > 0.05$ (see Table 2.1).

Acquisition. The number of trials required by each group to obtain the criterion of 20 correct responses is shown in Figure 2.1A. 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, $F(1, 69) = 21.98$, $p < .001$. The main effect of ELS was marginal, $F(1, 69) = 3.97$, $p = .050$. 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, $F(1, 69) = 0.38$, $p = .542$.

The expectation of reward during acquisition is shown in Figure 2.1B. Participants assigned to the continuous reinforcement schedule had a higher expectation of reward compared with participants learning under partial reinforcement, $F(1, 69) = 32.90$, $p < .001$. The main effect of ELS was also significant, $F(1, 69) = 4.67$, $p = .034$, such that the expectation of reward was higher in the non-ELS group than in the ELS group. The interaction was not significant, $F(1, 69) = 0.93$, $p = .339$.

Extinction. The extinction behavior of each group in Experiment 1 is shown in Figures 2.2A (extinction means) and 2.3 (extinction time courses). We observed a significant main effect of reinforcement schedule on the number of correct (previously rewarded) responses made in extinction, $F(1, 69) = 97.63$, $p < .001$. 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, $F(1, 69) = 1.83$, $p = .180$, and the interaction between ELS and schedule was not significant, $F(1, 69) = 2.67$, $p = .107$. 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, $F(1, 69) = 0.04$, $p = .844$. In the partial reinforcement condition, however, the effect of ELS was significant, $F(1, 69) = 4.41$, $p = .039$, 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 2.2B. In contrast to the pattern found during acquisition, participants trained on a partial reinforcement schedule had a higher expectation of reward, $F(1, 69) = 5.69$, $p = .020$. The main effect of ELS was also significant, $F(1, 69) = 5.38$, $p = .023$, such that the expectation of reward was higher in the non-ELS group than in the ELS group. The interaction effect was not significant, $F(1, 69) = 0.01$, $p = .905$.

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 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 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 2.1. There was a significant effect of ELS on the HADS anxiety subscale, $F(2, 209) = 4.61$, $p = .011$. Pairwise comparisons indicated that this effect was driven by higher anxiety in the high-ELS group compared to the non-ELS group, $F(1, 209) = 9.14$, $p = .003$. The moderate-ELS group did not differ from the non-ELS group, $F(1, 209) = 0.93$, $p = .335$. 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), $p > .05$.

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, $F(2, 100) = 2.18$, $p = .118$.

Acquisition. Acquisition data from Experiment 2 are shown in Figure 2.4. Consistent with Experiment 1 and previous studies, we observed slower acquisition in participants who received partial reinforcement compared to participants who received continuous reinforcement, $F(1, 200) = 52.47$, $p < .001$. There was also a significant effect of ELS on the number of acquisition trials, $F(2, 200) = 4.40$, $p = .014$, and a significant interaction between reinforcement schedule and ELS, $F(2, 200) = 4.77$, $p = .009$. The effect of ELS on acquisition was highly significant for participants trained under partial reinforcement, $F(2, 200) = 9.18$, $p < .001$, but was not significant for participants trained under continuous reinforcement, $F(2, 200) = 0.01$, $p = .986$. In the partial reinforcement condition, high-ELS participants required significantly more acquisition trials than both non-ELS participants, $F(1, 200) = 18.28$, $p < .001$, and moderate-ELS participants, $F(1, 200) = 9.24$, $p = .003$. The difference between non-ELS participants and moderate-ELS participants under partial reinforcement was not significant, $F(1, 200) = 2.25$, $p = .135$.

The main effect of the secondary task was not significant, and there were no significant interactions between task and the other factors, smallest $p > .05$.

Extinction. Extinction data from Experiment 2 are shown in Figures 2.5 (extinction means) and 2.6 (extinction time courses). Overall, there was a significant main effect of reinforcement schedule on extinction responding, with higher responding after partial reinforcement, $F(1, 200) = 92.43$, $p < .001$. This replicates the PREE observed in Experiment 1 and previous studies. We did not observe main effects of ELS, $F(2, 200) = 1.03$, $p = .358$, or of task, $F(1, 200) = 0.32$, $p = .572$. The three-way interaction between schedule, ELS, and task was also not significant, $F(2, 200) = 1.59$, $p = .207$. 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, $F(2, 200) = 3.10$, $p = .047$. 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, $F(1, 200) = 5.76$, $p = .017$, and the moderate-ELS single-task group, $F(1, 200) = 4.57$, $p = .034$. There was not a significant difference between the non-ELS single-task group and the moderate-ELS single-task group, $F(1, 200) = 0.11$, $p = .740$.

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, $F(1, 200) = 0.07$, $p = .796$. In the high-ELS group, the interaction between task and schedule was also non-significant, $F(1, 200) = 0.42$, $p = .518$. 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, $F(1, 200) = 4.00$, $p = .047$. This interaction was characterized by a numerical increase in persistence after continuous reinforcement, $F(1, 200) = 2.69$, $p = .103$, and a numerical decrease in persistence after partial reinforcement, $F(1, 200) = 1.43$, $p = .233$, 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.

Acknowledgment

The authors thank Katherine Misogas for research assistance.

Tables and Figures

Table 2.1

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)

Note. 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 Questionnaire (Felitti et al., 1998; Anda et al., 2006).

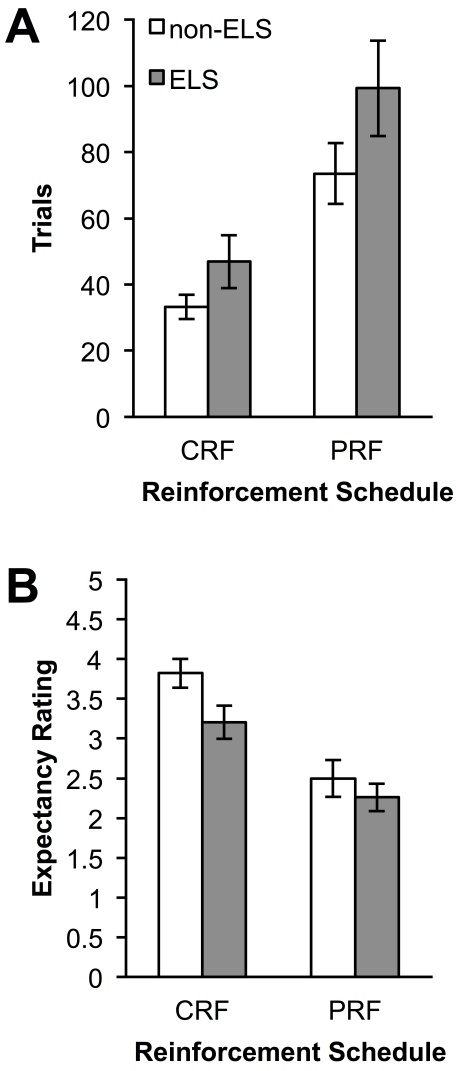

Figure 2.1. Experiment 1: Effects of early-life stress (ELS) and reinforcement schedule on acquisition behavior. Mean (± SEM) number of trials required to reach the criterion of 20 correct responses (A) and expectation of reward given for each trial on a scale of 1–5 (B). CRF, continuous reinforcement (100% of correct responses rewarded); PRF, partial reinforcement (50% of correct responses rewarded).

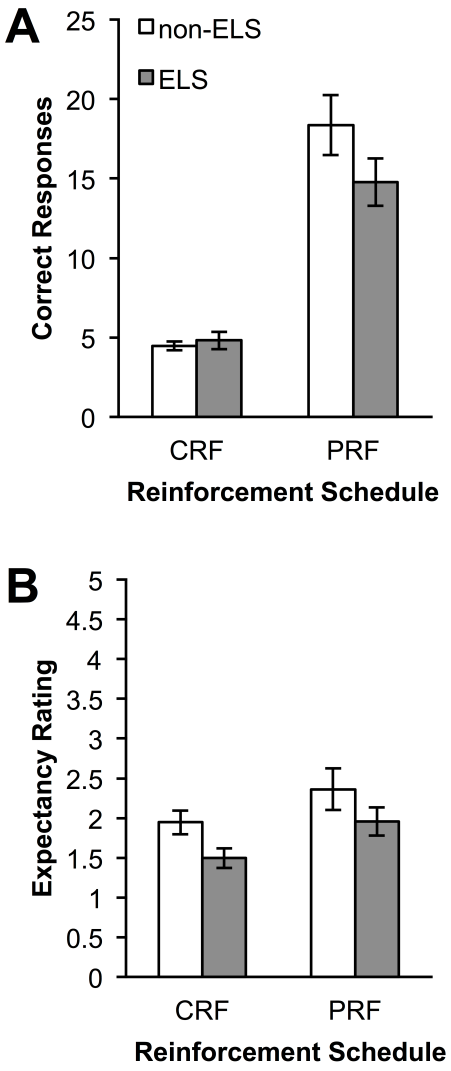

Figure 2.2. Experiment 1: Effects of early-life stress (ELS) and reinforcement schedule on extinction behavior. Mean (± SEM) number of correct responses (A) and expectation of reward given for each trial on a scale of 1–5 (B). CRF, continuous reinforcement (100% of correct responses rewarded); PRF, partial reinforcement (50% of correct responses rewarded).

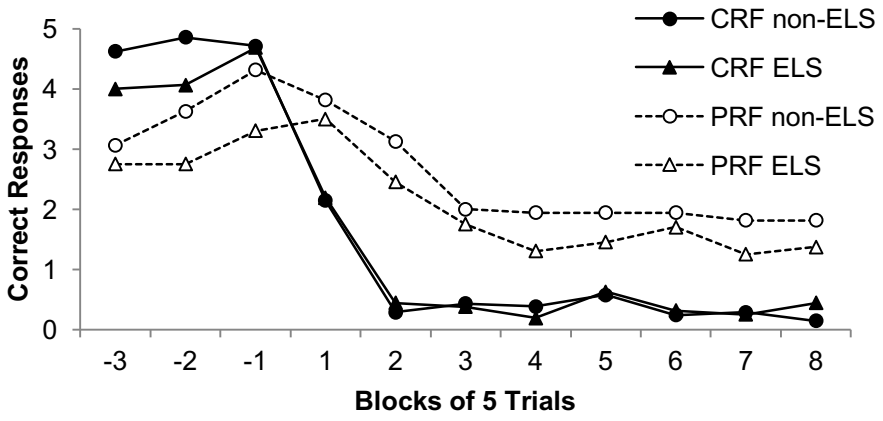

Figure 2.3. Experiment 1: Effects of early-life stress (ELS) and reinforcement schedule on extinction behavior by block. Extinction timecourses are shown, beginning with the last three blocks of acquisition. CRF = continuous reinforcement (100% of correct responses rewarded), PRF = partial reinforcement (50% of correct responses rewarded).

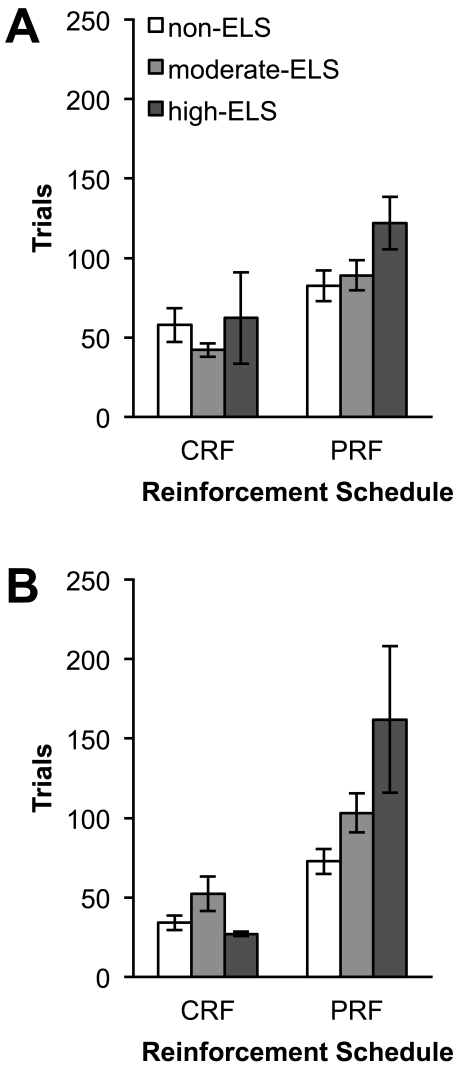

Figure 2.4. Experiment 2: Effects of early-life stress (ELS), reinforcement schedule, and distraction on acquisition behavior. Mean (± SEM) number of trials required to reach the criterion of 20 correct responses for participants in the single-task condition (A) and the dual-task condition (B). CRF, continuous reinforcement (100% of correct responses rewarded); PRF, partial reinforcement (50% of correct responses rewarded).

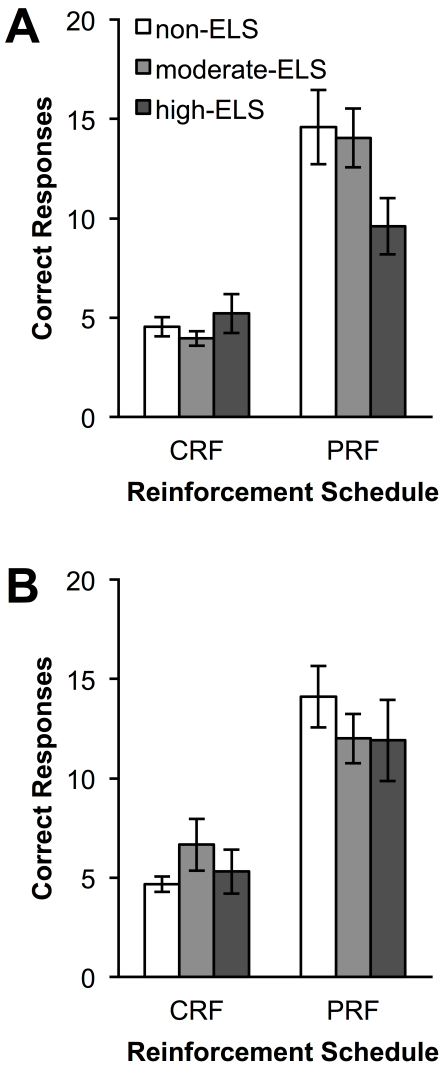

Figure 2.5. Experiment 2: Effects of early-life stress (ELS), reinforcement schedule, and distraction on extinction behavior. Mean (± SEM) number of correct responses for participants in the single-task condition (A) and the dual-task condition (B). CRF, continuous reinforcement (100% of correct responses rewarded); PRF, partial reinforcement (50% of correct responses rewarded).

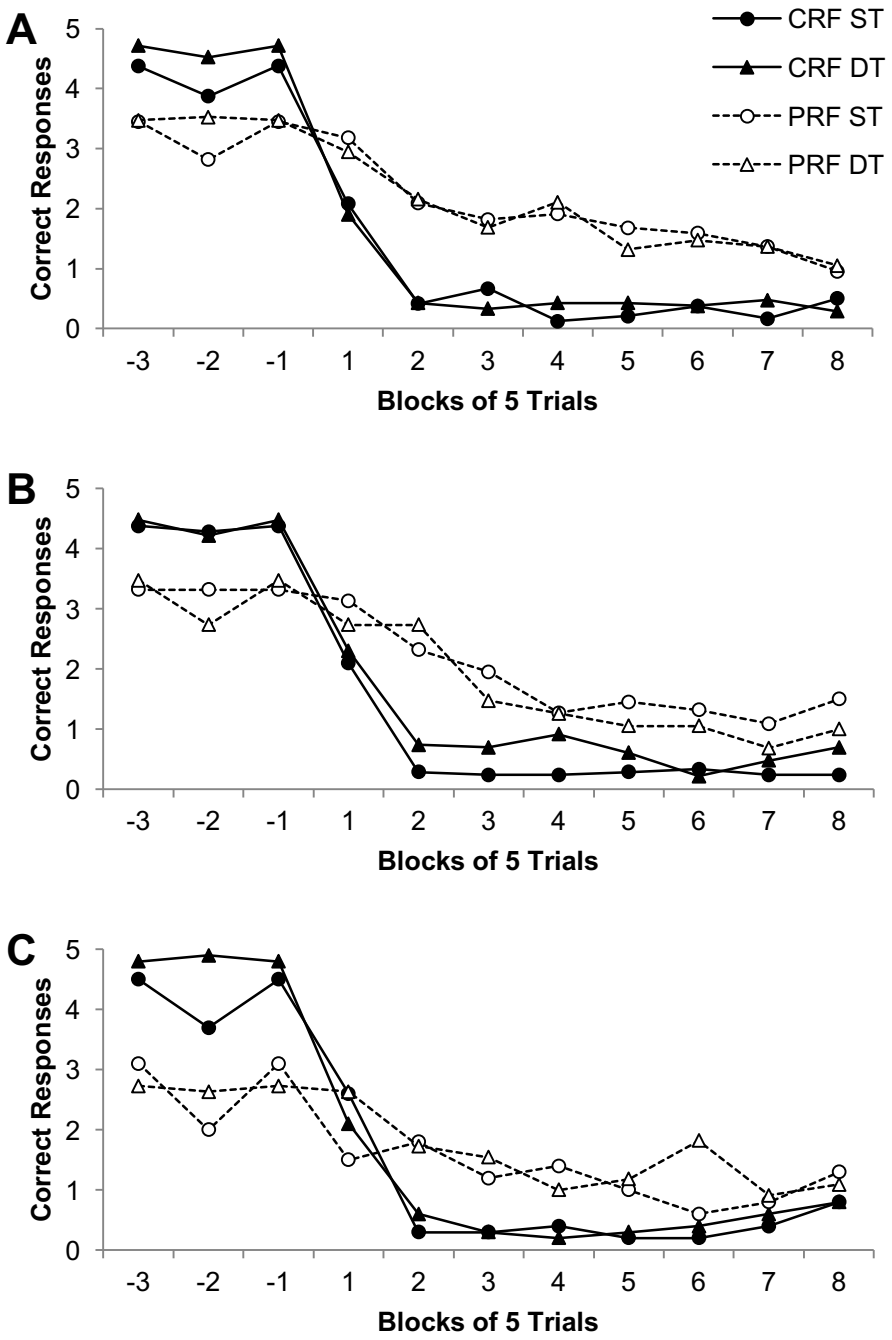

Figure 2.6. Experiment 2: Effects of early-life stress (ELS), reinforcement schedule, and distraction on extinction behavior by block. Extinction timecourses for the non-ELS (A), moderate-ELS (B) and high-ELS (C) groups are shown, beginning with the last three blocks of acquisition. CRF = continuous reinforcement (100% of correct responses rewarded), PRF = partial reinforcement (50% of correct responses rewarded), ST = single-task, DT = dual-task.

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CHAPTER 3

The Effect of Early-Life Stress on Avoidance Habit Learning

Introduction

The effects of stress on physical and psychological health have been of increasing interest in recent years, with one area of focus being the effects of stress that occurs during development, or early-life stress (ELS). Common sources of ELS are childhood abuse and neglect. Such experiences have been shown to cast a long shadow on health throughout the lifespan, affecting outcomes in adulthood ranging from obesity (Anda et al., 2006), heart disease (Dong et al., 2004), and liver disease (Dong et al., 2003) to sexually transmitted disease (Hillis et al., 2000) and depressive disorders (Chapman et al., 2004). The behavioral and neural mechanisms of these links between ELS and adult health are largely unknown. Because many negative health outcomes are linked to repetitive behaviors such as overeating or substance use, it is possible that an increased reliance on stimulus-response habits in this population could explain some of the health effects experienced by its constituents. Stimulus-response habits are instrumental behaviors that, in contrast to goal-directed actions, have come to be automatically elicited by contextual stimuli without regard to instrumental outcomes (Dickinson, 1985). For example, an animal that has learned the habit of pressing a lever to obtain a food reward will persist in lever pressing even after the food outcome has been devalued through selective satiation (Balleine and Dickinson, 1998), and there is evidence that humans also show insensitivity to outcome devaluation after overtraining of stimulus-response associations (Tricomi et al., 2009).

Stimulus-response habits can be appetitive (e.g., pressing a lever to receive a food reward) or avoidant (e.g., pressing a lever to avoid a shock). Most research on stimulus-response

habits has been conducted using appetitive habits, as the methods for evaluation of habit formation through devaluation tests have been well established. However, a recent study by Gillan and colleagues (2014) introduced a novel procedure for devaluation of aversive outcomes and demonstrated enhanced avoidance habits in people with obsessive-compulsive disorder. Like compulsions, negative health behaviors can be understood as avoidance habits, and we were therefore interested in whether adults with a history of ELS show an increased tendency to engage in avoidance habit behaviors in the lab. If so, this tendency could represent a behavioral vulnerability that increases the likelihood of the poor health outcomes observed in this group.

We used a noise avoidance task wherein participants could avoid hearing aversive noises delivered to the left and right ears by making the correct keyboard responses to associated warning stimuli (Fig. 3.1A). After learning the responses, participants underwent an instructed devaluation procedure in which one of the two earphones previously delivering aversive noises was removed (Fig. 3.1B), and then a test for habit formation was conducted in extinction. Avoidance habit formation was measured by whether the participant persisted in making the keyboard response associated with avoiding noise to the ear from which the earphone had been removed. In addition to testing for an effect of ELS, we also manipulated the level of training participants received (Experiment 1) and the level of distraction present during training (Experiment 2). The primary hypothesis of this study was that people who reported a history of ELS would show enhanced avoidance habits. The secondary hypotheses were (a) that people who receive a greater level of training prior to devaluation would show enhanced avoidance habits relative to people who received less training, and (b) that learning the stimulus-response associations in the presence of distraction would lead to enhanced avoidance habits relative to associations learned without distraction.

Experiment 1

Materials and Methods

Participants. Study participants were recruited from the undergraduate student population at the University of California, Los Angeles. Participants were compensated with credit toward partial fulfillment of course requirements. 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.

A total of 197 participants were recruited. Five people did not complete the experiment and one failed to follow the instructions, yielding a sample size of 191 (148 women, 43 men, M_{age} = 20.31 yr, SD_{age} = 1.80 yr, age range: 18-28 yr). We used the Childhood Trauma Questionnaire – Short Form (CTQ-SF; Bernstein et al., 2003) to assess participants' exposure to stress during their first 16 years of life. Participants were categorized as high-ELS and low-ELS based on whether they scored above or below the sample median.

Design and procedure. The avoidance learning task was adapted from procedures described in Gillan et al. (2014) and Gillan et al. (2015). Participants were instructed that their task was to avoid hearing aversive noises. Participants were shown two visual warning stimuli that predicted aversive noise to the left and right earphones, respectively, and were told that they could avoid hearing the aversive noises by making the correct keyboard responses when they saw the warning stimuli (Fig. 3.1A). Performing the correct response with the left hand avoided noise to the left earphone, and performing the correct response with the right hand avoided noise to the right earphone. A third stimulus was designated as the "safe" stimulus and never predicted aversive noise. Assignment of the three images to the three experimental trial types (warning stimulus 1, warning stimulus 2, and safe stimulus) was randomized across participants. On each

trial, one of the three stimuli was selected randomly and presented on screen for 500 ms. Correct responses to the warning stimuli prevented aversive noise from being delivered to the earphones, but did not terminate the stimulus. If the participant pressed the incorrect key or failed to respond within 500 ms, the aversive noise (an audio file resembling a female scream) was delivered to the corresponding earphone. Responses to the "safe" stimulus had no effect. There was a delay of 500 ms between termination of the warning stimulus and delivery of the aversive noise, and the intertrial interval was 2 s. Audio files were 1 s long and played at a volume of 82 dB.

Following demonstration of the stimulus-outcome contingencies, participants performed six practice trials (two per stimulus). Participants were allowed to repeat the practice phase if desired. The main experiment consisted of two phases, a training phase and a post-devaluation habit test. The amount of training was varied between subjects; participants in the short training condition completed 120 trials (40 per stimulus), and participants in the long training condition completed 600 trials (200 per stimulus). Assignment to condition was randomized across participants. After training was complete, one of the two outcomes was devalued by having participants remove one of the earphones (Fig. 3.1B). Which earphone was removed (left versus right) was counterbalanced across participants. Participants were told that they would be evaluated based on the responses they made to avoid noise to the earphone that had not been removed, and that it was not necessary to make the response associated with avoiding noise to the earphone that had been removed. The habit test was conducted in extinction (i.e., no noises were delivered to either earphone), but participants were not informed of this. The habit test consisted of 30 trials (10 per stimulus). The dependent variable of interest was whether the participant persisted in performing the response associated with avoiding aversive noise to the

removed earphone, as performance of this behavior was no longer of value and thus would be evidence of habit formation.

Participants completed the experiment in a private testing room on a Macintosh computer. Button press responses were made using the computer keyboard and were recorded with E-Prime Standard (Version 2.0) experimental software. Following completion of the computer task, participants completed a packet of questionnaires. The 28-item CTQ-SF (Bernstein et al., 2003) was used to assess stress exposure during the first 16 years of life. The items on the questionnaire ask about experiences of physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse. The 40-item State-Trait Anxiety Inventory (Spielberger, 1983) was used to assess anxiety at the present moment (state anxiety) and in general (trait anxiety). The 20-item Beck Depression Inventory-II (Beck et al., 1996) was used to assess depressive symptoms during the past two weeks (suicidality question omitted). The 44-item Big Five Inventory (John et al., 1991; John et al., 2008) was used to assess personality along the dimensions of extraversion, agreeableness, conscientiousness, neuroticism, and openness. Finally, the 10-item Perceived Stress Scale (Cohen et al., 1983) was used to assess how unpredictable, uncontrollable, and overloading participants' lives had been during the past month. The entire lab visit took approximately one hour.

Results

Sample characteristics are reported in Tables 3.1 and 3.2. The median score on the CTQ-SF used to block participants into low-ELS and high-ELS groups was 32.00. The low-ELS group had a mean score of 27.91 (SD = 2.18) and the high-ELS group had a mean score of 44.02 (*SD* = 12.33). The high-ELS group differed significantly from the low-ELS group on measures of state anxiety, $t(188) = 5.11$, $p < .001$, trait anxiety, $t(185) = 6.39$, $p < .001$, depression, $t(186) = 7.17$, p

< .001, extraversion, $t(189) = 2.77$, $p = .006$, agreeableness, $t(189) = 3.19$, $p = .002$, conscientiousness, $t(189) = 4.43$, $p < .001$, neuroticism, $t(189) = 4.56$, $p < .001$, and perceived stress, $t(185) = 3.70$, $p < .001$.

We tested for effects of the level of training (120 training trials versus 600 training trials) and level of ELS (low-ELS versus high-ELS) on responding during training and during the post-devaluation habit test. During training, response accuracy to the two warning stimuli was 81.2% (Fig. 3.2A and Fig. 3.3A), and the false alarm rate to the safe stimulus was 11.6% (Fig. 3.2B and Fig. 3.3B). Training accuracy did not differ significantly across levels of training, $F(1, 187) = 2.80$, $p = .096$, or levels of ELS, $F(1, 187) = 0.78$, $p = .378$, and the interaction between training and ELS was not significant, $F(1, 187) = 0.69$, $p = .407$. False alarm rate also did not differ significantly across levels of training, $F(1, 187) = 0.08$, $p = .775$, or levels of ELS, $F(1, 187) = 0.08$, $p = .774$, and the interaction between training and ELS was not significant, $F(1, 187) < 0.01$, $p = .969$.

During the post-devaluation habit test, 100% of participants responded to the valued stimulus, with an average response rate of 90.7%. Responding to the valued stimulus did not differ significantly across levels of training, $F(1, 187) = 2.60$, $p = .109$, or levels of ELS, $F(1, 187) = 2.60$, $p = .109$, and the interaction between training and ELS was not significant, $F(1, 187) = 1.30$, $p = .255$.

We tested for habit behavior by conducting the chi-square test on the number of participants who responded to the devalued stimulus during the post-devaluation habit test. The effect of training was not significant, $\chi^2(1) = 0.04$, $p = 0.837$, and the effect of ELS was also not significant, $\chi^2(1) = 1.97$, $p = 0.161$. We then analyzed the data separately for participants who were instructed to remove the right earphone ($n = 96$) and participants who were instructed to

remove the left earphone (n = 95) during the devaluation procedure. This variable had been counterbalanced across participants, but there is evidence suggesting that people are more likely to engage in habit behaviors when they are using their dominant hand (Neal et al., 2011). In this analysis, there was no effect of training in the group that was instructed to remove the right earphone, $\chi^2(1) = 0.05$, $p = 0.832$, or in the group that was instructed to remove the left earphone, $\chi^2(1) = 0.01$, $p = 0.936$. We did, however, observe a significant effect of ELS in the group that was instructed to remove the right earphone, $\chi^2(1) = 4.26$, $p = 0.039$, such that 26.5% of the low-ELS group performed the habit response, while 46.8% of the high-ELS group performed the habit response (Fig. 3.4). This effect was not present in the group that was instructed to remove the left earphone, $\chi^2(1) = 0.01$, $p = 0.936$.

Finally, we investigated the effect of the amount of ELS on post-devaluation habit responding by calculating correlation coefficients for the relationship between CTQ-SF score and the number of responses made to the devalued stimulus. This effect was not significant in either the group instructed to remove the right earphone, $R = .067$, $p = .516$, or the group instructed to remove the left earphone, $R = -.007$, $p = .948$. A scatter plot from the group instructed to remove the right earphone is provided in Figure 3.5 for illustration and comparison with Experiment 2.

Experiment 2

In Experiment 1, we found support for the hypothesis that ELS is associated with enhanced avoidance habits, but this effect was only observed in the subset of participants who were tested for habit behavior in the right hand. Therefore, in Experiment 2, we sought to replicate the effect of ELS observed in Experiment 1, and we also added a condition in which participants performed the avoidance learning task under distraction. Because the effect in

Experiment 1 was isolated to those people tested for habit behavior in the right hand, all participants in Experiment 2 were tested for habit behavior in the right hand by having them remove the right earphone during the devaluation procedure.

Materials and Methods

Participants. As in Experiment 1, study participants were recruited from the undergraduate student population at the University of California, Los Angeles. Participants were compensated with credit toward partial fulfillment of course requirements. 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.

A total of 119 participants were recruited. One person was excluded for failure to follow instructions, yielding a sample size of 118 (95 women, 23 men, M_{age} = 20.52 yr, SD_{age} = 1.60 yr, age range: 18-26 yr). As in Experiment 1, we used the CTQ-SF (Bernstein et al., 2003) to assess participants' exposure to stress during their first 16 years of life. Participants were categorized as high-ELS and low-ELS based on whether they scored above or below the sample median.

Design and procedure. Participants performed the avoidance learning task described above in Experiment 1 (Fig. 3.1A). We manipulated the level of distraction within subjects during the training phase of the experiment by having participants perform a counting task during alternate blocks of 30 trials. During counting blocks, participants were randomly shown an image of a dog or a cat for 500 ms after each noise avoidance trial. They were instructed to count the cats and ignore the dogs. At the end of each counting block, participants were asked to report how many cats they had counted in the previous block. Before beginning the main experiment, participants completed practice trials on both the avoidance task and the counting task, and were allowed to repeat the practice trials if desired. To minimize task difficulty, we

increased the response window for the noise avoidance task from 500 ms to 750 ms. Six stimulus images were used for the noise avoidance task, such that the same three stimuli were shown during all counting blocks and the other three stimuli were shown during non-counting blocks. Participants completed a total of 360 training trials (180 trials per level of distraction).

The devaluation procedure was the same as in Experiment 1 (Fig. 3.1B), except that in Experiment 2 we instructed all participants to remove the right earphone. The post-devaluation habit test consisted of 60 trials, 30 containing stimuli that had been learned in the no-distraction condition and 30 containing stimuli that had been learned in the distraction condition. The 60 stimuli were presented in random order. Participants were not required to perform the counting task during the habit test. As in Experiment 1, the dependent variable of interest was whether the participant persisted in performing the response associated with avoiding aversive noise to the removed earphone.

Participants completed the experiment in a private testing room on a Macintosh computer. Button press responses were made using the computer keyboard and were recorded with E-Prime Standard (Version 2.0) experimental software. Following completion of the computer task, participants completed the same packet of questionnaires described above for Experiment 1. The entire lab visit took approximately one hour.

Results

Sample characteristics are reported in Tables 3.1 and 3.2. The median score on the CTQ-SF used to block participants into low-ELS and high-ELS groups was 32.50. The low-ELS group had a mean score of 28.22 (SD = 2.07) and the high-ELS group had a mean score of 42.66 (*SD* = 8.71). The high-ELS group differed significantly from the low-ELS group on measures of state anxiety, $t(113) = 3.32$, $p = .001$, trait anxiety, $t(115) = 3.48$, $p = .001$, depression, $t(114) = 3.90$, p

< .001, agreeableness, $t(116) = 3.16$, $p = .002$, neuroticism, $t(116) = 2.21$, $p = .029$, and perceived stress, $t(112) = 2.73$, $p = .007$.

We tested for effects of the level of distraction (no-distraction versus distraction) and level of ELS (low-ELS versus high-ELS) on responding during training and during the post-devaluation habit test. During training, response accuracy to the four warning stimuli was 91.8% (Fig. 3.6A), and the false alarm rate to the two safe stimuli was 9.3% (Fig. 3.6B). There was a significant effect of distraction on training accuracy, $F(1, 116) = 15.60$, $p < .001$, such that accuracy was higher in single-task condition blocks (92.7%) than in dual-task condition blocks (90.8%). Training accuracy did not differ significantly across levels of ELS, $F(1, 116) = 0.28$, $p = .599$, and the interaction between distraction and ELS was not significant, $F(1, 116) = 0.06$, $p = .811$. False alarm rate did not differ significantly across levels of distraction, $F(1, 116) = 0.74$, $p = .390$, or levels of ELS, $F(1, 116) = 3.79$, $p = .054$, and the interaction between distraction and ELS was not significant, $F(1, 116) = 0.23$, $p = .630$. The direction of the marginal effect of ELS was toward a higher rate of false alarms in the high-ELS group (12.6%) than the low-ELS group (6.0%).

During the post-devaluation habit test, 100% of participants responded to the valued stimuli, with an average response rate of 92.7%. Responding to valued stimuli did not differ significantly across levels of distraction, $F(1, 116) = 0.11$, $p = .740$, or levels of ELS, $F(1, 116) = 0.12$, $p = .727$, and the interaction between distraction and ELS was not significant, $F(1, 116) = 3.73$, $p = .056$. The direction of the marginal interaction between distraction and ELS was toward higher responding to valued stimuli learned in the no-distraction condition (94.1%) than the distraction condition (92.0%) in the low-ELS group, and toward higher responding to valued

stimuli learned in the distraction condition (93.7%) than the no-distraction condition (90.8%) in the high-ELS group.

We tested for habit behavior by conducting McNemar's chi-square test for within-subject designs and the chi-square test on the number of participants who responded to the devalued stimuli during the post-devaluation habit test. The effect of distraction was not significant, $\chi^2(1) = 0.25$, $p = 0.617$. Consistent with Experiment 1, we again observed a significant effect of ELS, $\chi^2(1) = 7.66$, $p = 0.006$, such that 33.9% of the low-ELS group performed the habit response, while 59.3% of the high-ELS group performed the habit response (Fig. 3.7).

Finally, we investigated the effect of the amount of ELS on post-devaluation habit responding by calculating correlation coefficients for the relationship between CTQ-SF score and the number of responses made to the devalued stimulus. This relationship was significant, $R = .203$, $p = .027$. The scatter plot is shown in Figure 3.8. As can be seen in the figure, the data do not conform to a linear pattern but rather fall into two clusters of participants: people who made five or fewer responses to the devalued stimuli and people who made 15 or more such responses. These clusters may represent people who made no devalued responses or made the devalued response inadvertently (i.e., because of inhibition failure), and people who made a conscious decision not to attempt inhibition of the devalued response during the habit test.

Discussion

In two experiments using an avoidance learning task, we observed evidence of enhanced avoidance habits in adults who reported a history of ELS. Interestingly, this effect was only present when the avoidance habit was measured in the right hand, consistent with previous observations that people are more likely to exhibit habits when they are executing behaviors with their dominant hand (Neal et al., 2011). Our findings are consistent with previous work from our

lab showing enhanced appetitive habit behavior in people who have a history of ELS (Patterson et al., 2013), and the observed enhanced avoidance habit behavior may contribute to the negative health outcomes commonly experienced by this population. Negative health outcomes are frequently tied to negative health behaviors, which may be performed habitually. Certain negative health behaviors such as overeating and substance use can be conceptualized as avoidance behaviors, which over time can become avoidance habits. For example, people may initially engage in overeating or substance use in a goal-directed manner to avoid feelings of distress, but over time these behaviors may become more automatic and stimulus-bound.

A possible biological basis for enhanced habit behavior following ELS is that stress selectively damages the neural structures that support goal-directed behavior, which could lead to a compensatory over-reliance on habit responding. Goal-directed behavior relies on prefrontal cortex, dorsomedial striatum, and the hippocampus, which have been shown to atrophy following stress exposure (Dias-Ferreira et al., 2009; Joëls et al., 2007; McEwen, 2000; Soares et al., 2012). Habit behavior, on the other hand, appears to rely on the dorsolateral striatum (Yin et al., 2004), which is less sensitive to stress and indeed has been shown in some cases to undergo stress-induced hypertrophy (Dias-Ferreira et al., 2009; Soares et al., 2012). The extent to which these morphological changes are reversible is not known. The presence of significant stress during a sensitive period of development may crystallize these dynamics, setting the stage for an overreliance on habit responding in adulthood. Some evidence supporting this hypothesis includes the finding that male rats exposed to maternal separation during the first two weeks of life are more likely to use a stimulus-response navigation strategy in early adolescence (Grissom et al., 2012), and people exposed to stress prenatally are more likely to use a stimulus-response

navigation strategy in adulthood (Schwabe et al., 2012). Future research incorporating neuroimaging of habit learning in the ELS population should investigate this possibility.

In addition to providing support for the hypothesis that ELS alters the tendency toward habit responding, the results of the present study also demonstrate the utility of avoidance learning tasks in human habit research. Research on habits in humans has traditionally been carried out in appetitive situations with participants working for monetary rewards, points, or food (e.g., Tricomi et al., 2009), but tasks employing aversive stimuli have a long history of success in the nonhuman animal habit learning literature, particularly in maze navigation tasks where animals are motivated to escape a negative situation such as a water tank or open surface (e.g., McDonald and White, 1994; Packard and McGaugh, 1992). Aversive stimuli like the scream sound used in the present study are not difficult to incorporate into computer-based tasks and may provide greater motivation than appetitive stimuli.

Two hypotheses that we made in this pair of experiments were not borne out by the results. In Experiment 1, we predicted that a longer period of training would result in greater habit responding, and in Experiment 2, we predicted that distraction during habit formation would result in greater habit responding. Neither of these manipulations affected the level of habit formation as measured by our post-devaluation habit test. It is possible that the manipulations we employed were not effective because the manipulations were not strong enough. Our manipulation of amount of training was a five-fold increase in the number of training trials, but participants in the long training condition still received only a single training session, and it is possible that to see an effect of training, multiple sessions would be required. An experiment conducted with appetitive stimuli that showed an effect of training on habit responding implemented 12 training sessions over the course of three days (Tricomi et al., 2009).

Similarly, the distraction task we used may have failed to provide enough of a challenge. Demonstration of such effects in future experiments will be an important step in validating our approach and interpretations.

One discrepancy in the results of this study is that we observed a positive correlation between amount of ELS and number of habit responses in Experiment 2 but not in Experiment 1. This is likely due to the fact that Experiment 2 (a) had more participants who had the right hand devalued (118 versus 96) and (b) had a longer extinction block, allowing for more opportunity to make the habit response. The clustering of participants into two groups may represent differing strategic approaches to the task, and should be investigated in future research.

A limitation of this study is that because we used a college sample, our ELS groups may be more high-functioning and resilient to stress than people with a history of ELS in the general population. Nevertheless, even this sample yielded evidence in support of our hypothesis that ELS affects avoidance habit formation. Future research with a more representative sample would, however, yield important information about the generalizability of our findings and typical effect sizes. A second limitation is that our sample was primarily composed of women; a sample with a larger proportion of men would be necessary to demonstrate that ELS has similar effects on avoidance habits in both genders.

Our findings extend recent work demonstrating enhanced avoidance habits in people with obsessive-compulsive disorder (Gillan et al., 2014), identifying a second population with this behavioral pattern. Additional populations that may show similar patterns include people with post-traumatic stress disorder, binge eating disorder, and substance use disorders. Future research should investigate these possibilities. The present experiments have implications for the development of interventions aimed at reducing the detrimental effects of ELS. Enhanced

avoidance habit formation may be related not only to behavioral habits such as overeating and substance abuse but also psychological habits such as avoidant thought and dissociation, and interventions geared toward minimizing such habits may have substantial effects on the quality of life of people who struggle to overcome them.

Acknowledgments

The authors thank Ling Lee Chong, Zhixi Liu, and Alex Gordon for research assistance.

Tables and Figures

Table 3.1

Sample characteristics

	Experiment 1		Experiment 2	
	Low-ELS	High-ELS	Low-ELS	High-ELS
CTQ-SF	27.91 (2.18)	44.02 (12.33)	28.22 (2.07)	42.66 (8.71)
STAI				
State anxiety	36.38 (10.98)	44.77 (11.62)	35.19 (13.06)	43.07 (12.38)
Trait anxiety	38.43 (9.77)	48.58 (11.87)	40.95 (11.73)	48.36 (11.33)
BDI-II	7.32 (5.67)	16.23 (10.64)	7.43 (7.82)	13.72 (9.48)
BFI				
Extraversion	3.29 (0.91)	2.95 (0.79)	3.22 (0.89)	2.99 (0.87)
Agreeableness	3.98 (0.55)	3.71 (0.63)	3.95 (0.57)	3.57 (0.73)
Conscientiousness	3.77 (0.50)	3.38 (0.70)	3.70 (0.67)	3.48 (0.67)
Neuroticism	2.84 (0.74)	3.33 (0.74)	2.99 (0.81)	3.33 (0.86)
Openness	3.35 (0.65)	3.36 (0.57)	3.42 (0.66)	3.45 (0.67)
PSS	17.03 (6.32)	20.52 (6.54)	16.71 (6.76)	20.28 (7.16)

Note. Mean (SD) scores on questionnaire measures for participants grouped by reported level of childhood stress exposure. ELS = early-life stress; CTQ-SF = Childhood Trauma Questionnaire – Short Form (Bernstein et al., 2003); STAI = State-Trait Anxiety Inventory (Spielberger, 1983); BDI-II = Beck Depression Inventory-II (Beck et al., 1996); BFI = Big Five Inventory (John et al., 1991; John et al., 2008); PSS = Perceived Stress Scale (Cohen et al., 1983).

Table 3.2

Prevalence of early-life stress (ELS) in sample by type of stress

	Experiment 1					Experiment 2				
	5	6-10	11-15	16-20	21-25	5	6-10	11-15	16-20	21-25
CTQ-SF subscale										
Physical abuse	62.8%	30.9%	4.7%	0.5%	1.0%	58.5%	35.6%	3.4%	2.5%	0.0%
Physical neglect	47.1%	43.5%	8.4%	1.0%	0.0%	51.7%	47.5%	0.8%	0.0%	0.0%
Emotional abuse	31.4%	48.2%	14.1%	2.6%	3.7%	24.6%	55.9%	12.7%	6.8%	0.0%
Emotional neglect	27.7%	46.6%	17.3%	6.8%	1.6%	28.0%	46.6%	17.8%	6.8%	0.8%
Sexual abuse	84.3%	11.0%	2.1%	2.1%	0.5%	84.7%	9.3%	3.4%	0.8%	1.7%

Note. Percentage of participants in each experiment broken down by level and type of childhood stress reported. For each subscale, five is the lowest score, corresponding to a response of "never" for each item. CTQ-SF = Childhood Trauma Questionnaire – Short Form (Bernstein et al., 2003).

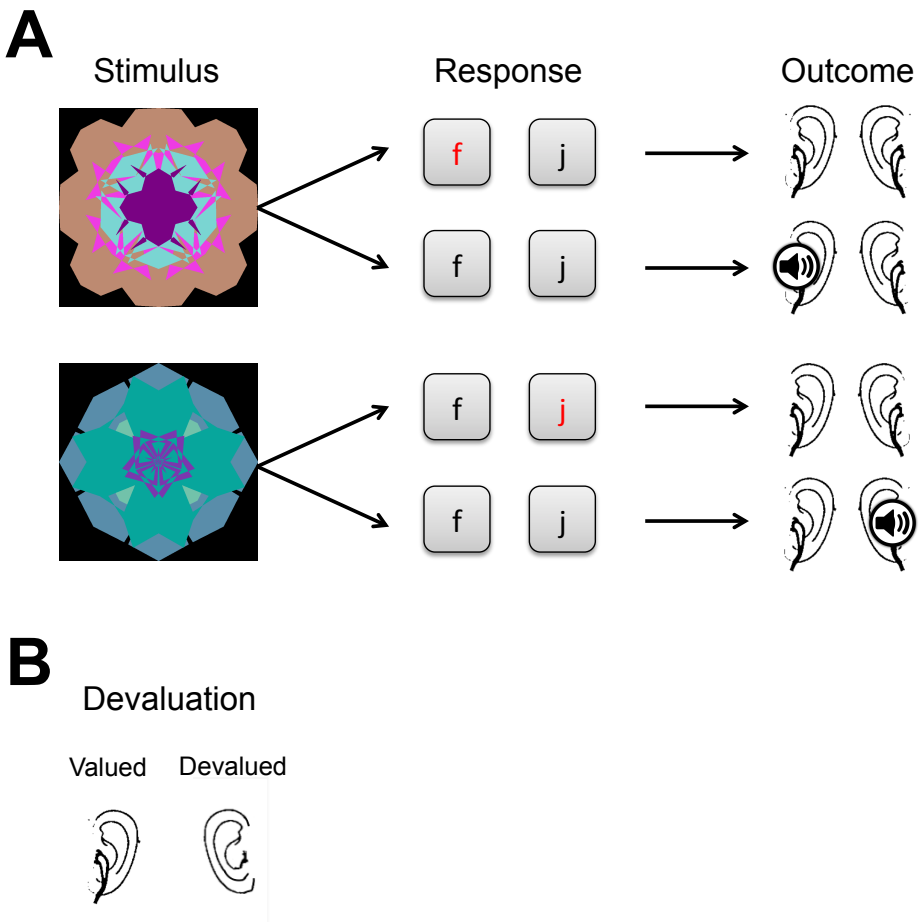

Figure 3.1. Experimental procedure. (a) Participants learned to make avoidance responses to two warning stimuli that predicted aversive noise played to the left (top) and right (bottom) earphones. If the correct avoidance response (shown in red) was made in time, the aversive noises were not delivered. (b) After training, one of the two outcomes was devalued by having participants remove one of the two earphones.

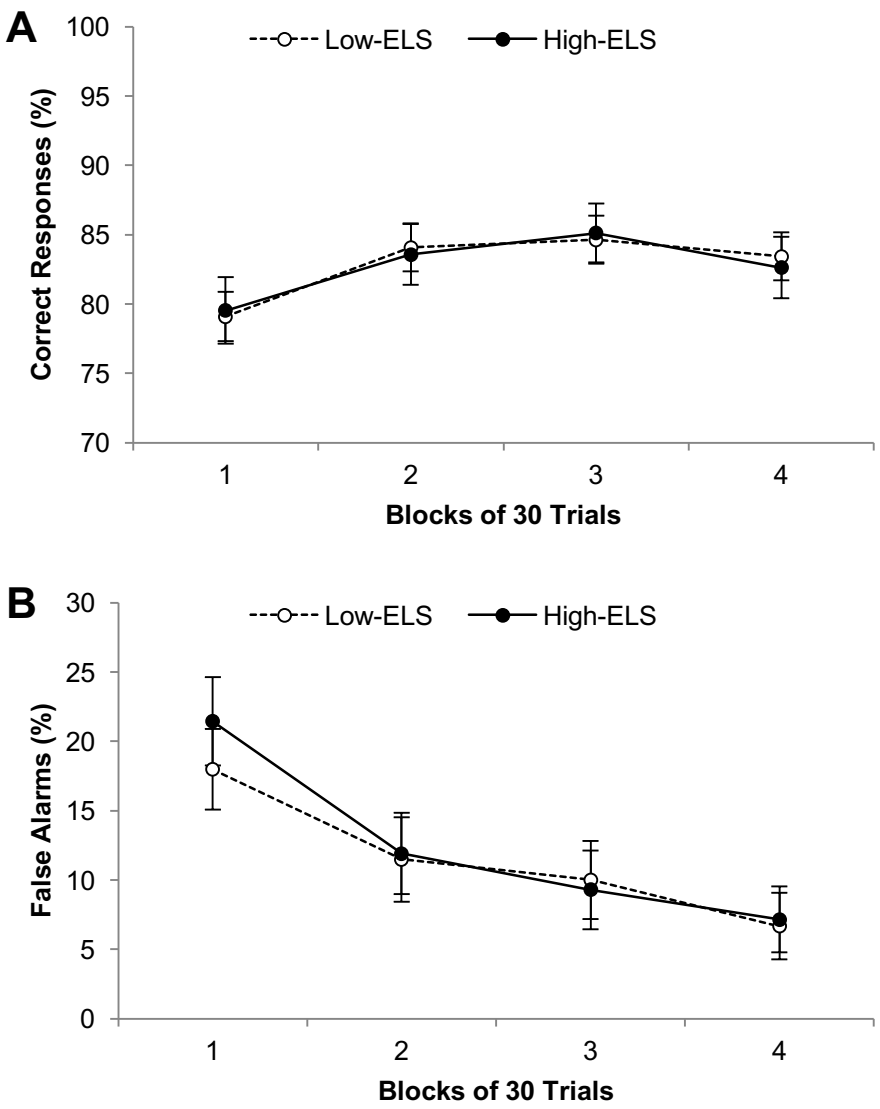

Figure 3.2. Experiment 1: Effects of early-life stress (ELS) on acquisition behavior by block, short training condition. Timecourses show % correct avoidance responses to the warning stimuli (A) and % false alarms to the safe stimulus (B) during the training phase.

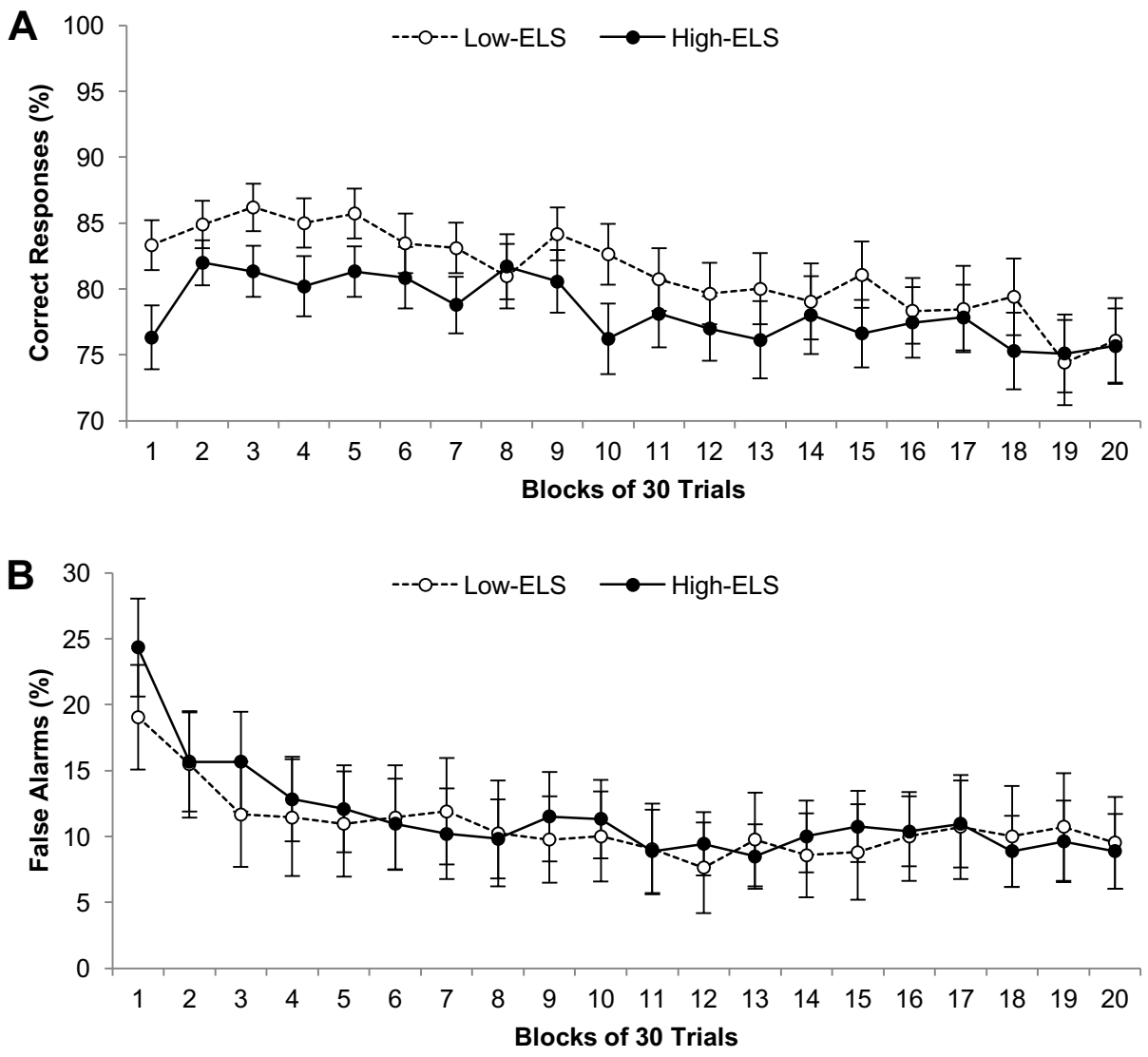

Figure 3.3. Experiment 1: Effects of early-life stress (ELS) on acquisition behavior by block, long training condition. Timecourses show % correct avoidance responses to the warning stimuli (A) and % false alarms to the safe stimulus (B) during the training phase.

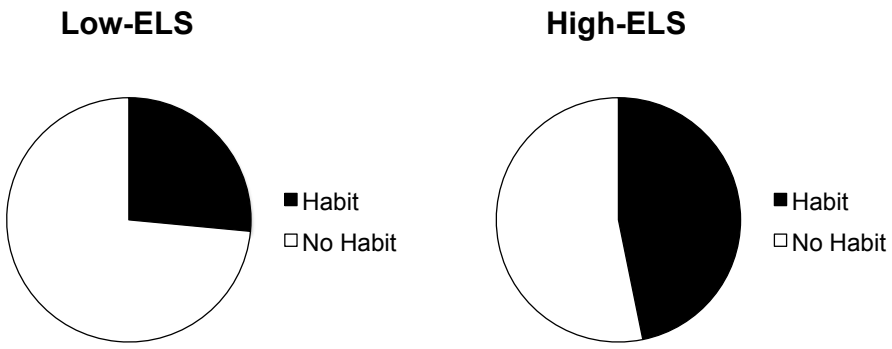

Figure 3.4. Experiment 1: Effects of early-life stress (ELS) on proportion of sample exhibiting avoidance habit behavior. Participants were scored as exhibiting habit behavior if they continued to respond to the devalued stimulus during the post-devaluation habit test.

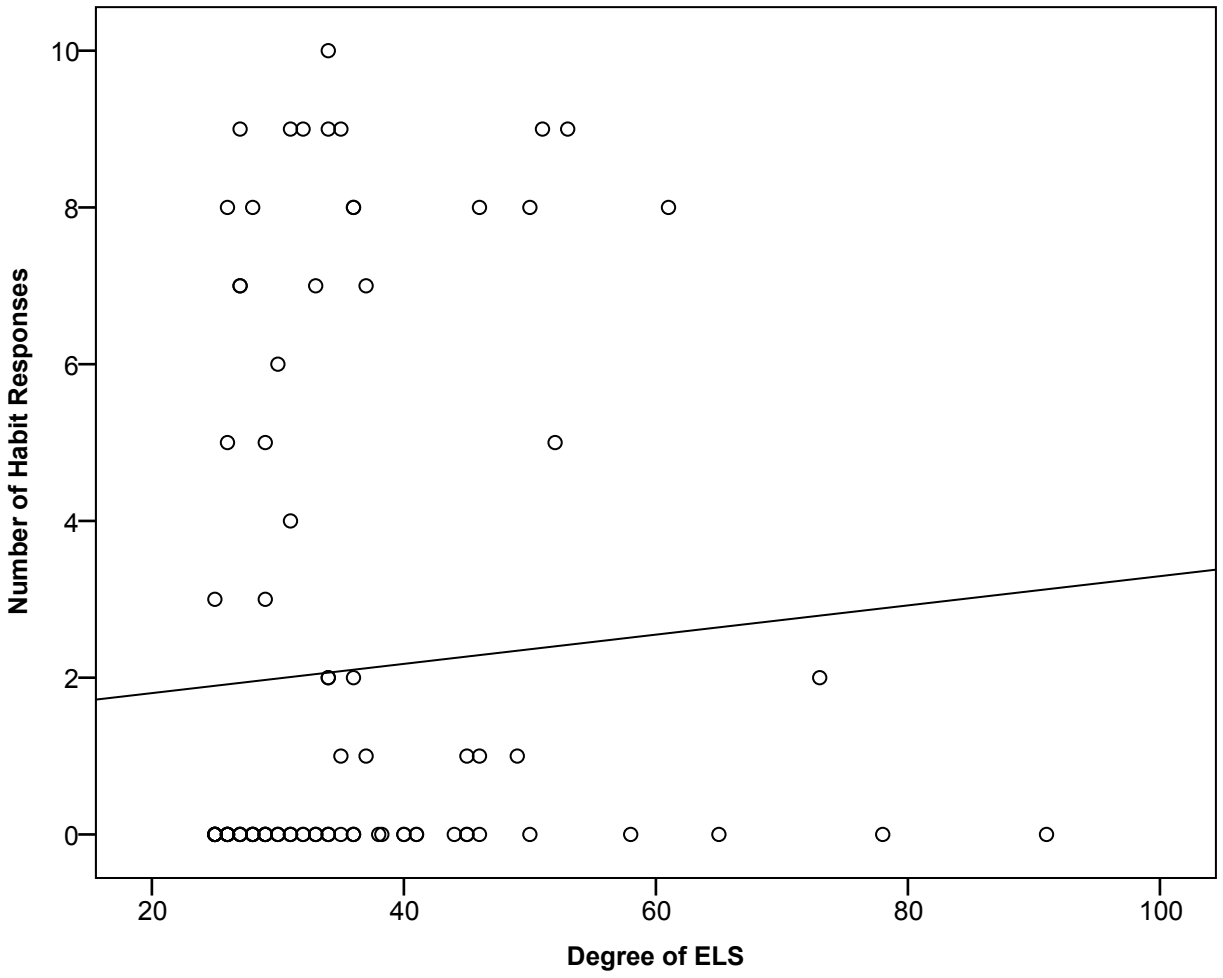

Figure 3.5. Experiment 1: Relationship between degree of early-life stress (ELS) and number of avoidance habit responses made on the post-devaluation habit test.

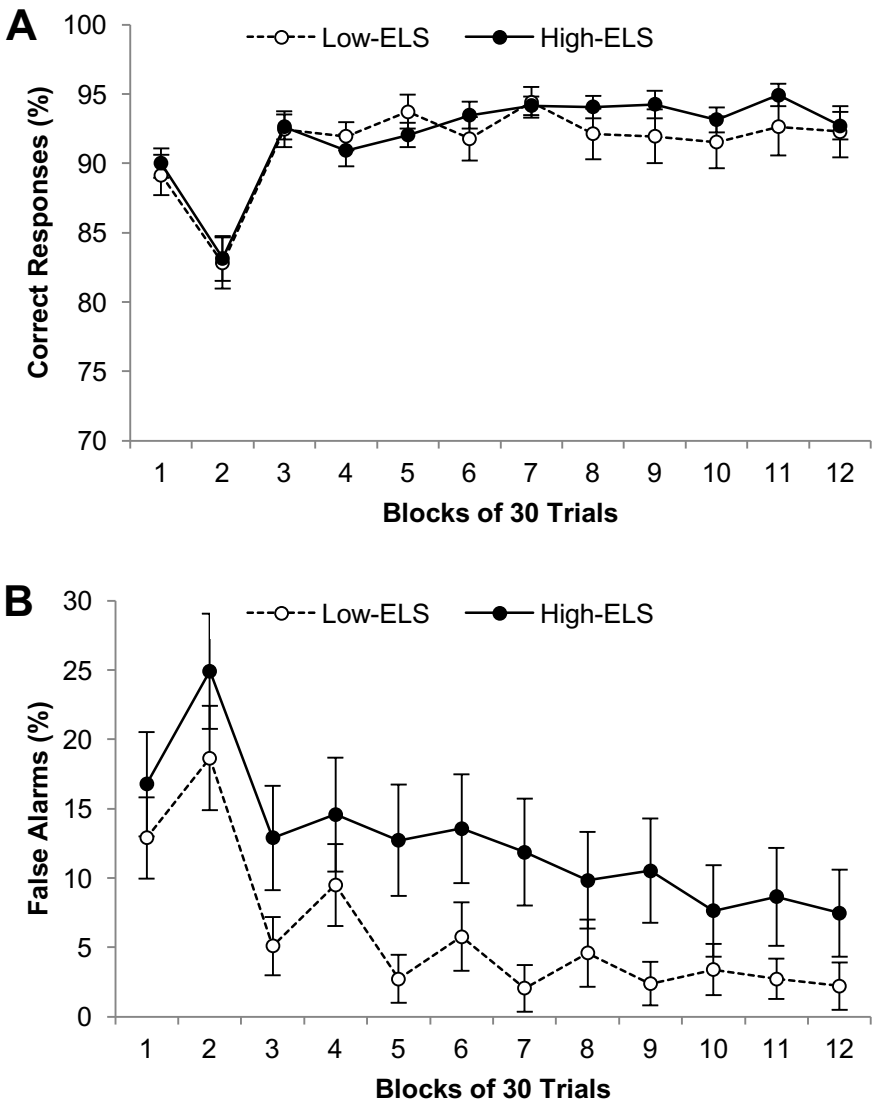

Figure 3.6. Experiment 2: Effects of early-life stress (ELS) on acquisition behavior by block. Timecourses show % correct avoidance responses to the warning stimuli (A) and % false alarms to the safe stimuli (B) during the training phase. Odd blocks were performed under single-task conditions (no-distraction) and even blocks were performed under dual-task conditions (distraction).

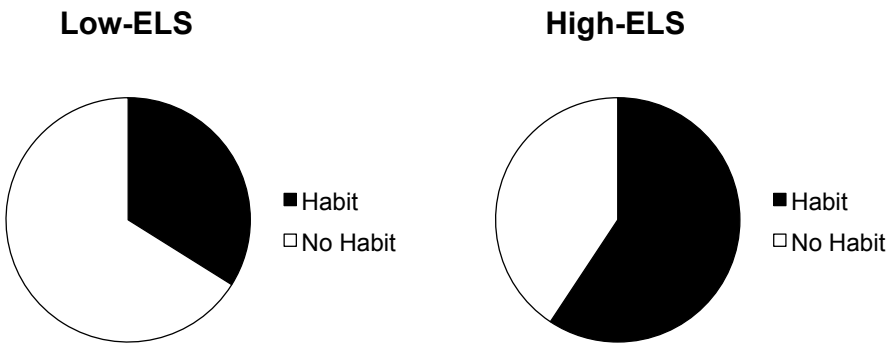

Figure 3.7. Experiment 2: Effects of early-life stress (ELS) on proportion of sample exhibiting avoidance habit behavior. Participants were scored as exhibiting habit behavior if they continued to respond to the devalued stimulus during the post-devaluation habit test.

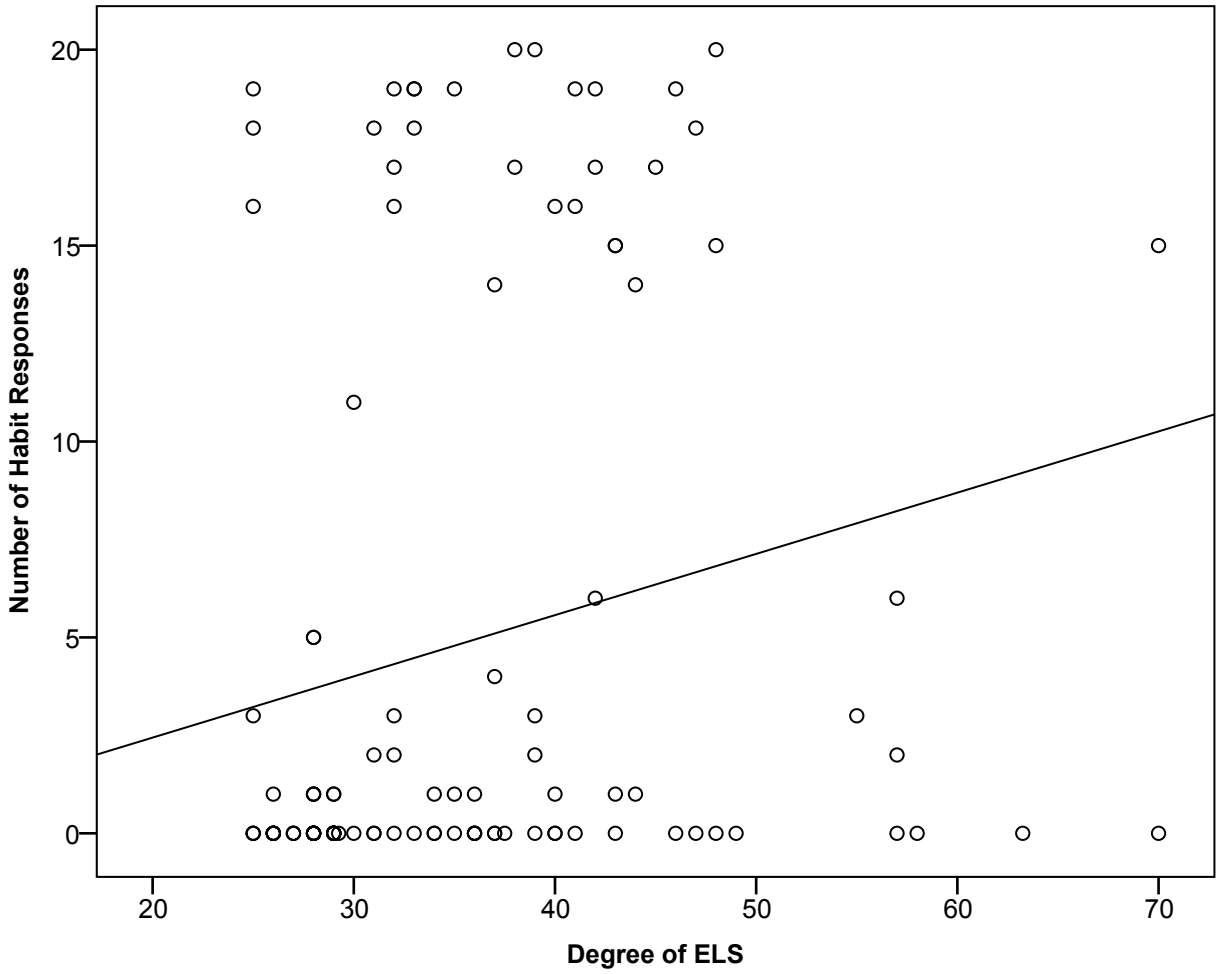

Figure 3.8. Experiment 2: Relationship between degree of early-life stress (ELS) and number of avoidance habit responses made on the post-devaluation habit test.

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CHAPTER 4

A Coordinates-Based Meta-Analysis of Human Habit Learning

Introduction

Localization of the neural substrates of habitual responding is an ongoing effort with important implications for our understanding of maladaptive behaviors such as drug addiction (Everitt and Robbins, 2005). Lesion studies in non-human animals (e.g., Fernandez-Ruiz et al., 2001; Packard et al., 1989) and neuropsychological studies in humans (e.g., Knowlton et al., 1996) have implicated the dorsal striatum in the development and expression of habitual behavior. In the rodent, there is evidence suggesting that within the dorsal striatum, the dorsolateral striatum (analogous to the putamen in the human brain) underlies habitual behavior while the dorsomedial striatum (analogous to the caudate in the human brain) underlies non-habitual, goal-directed behavior (Yin and Knowlton, 2004; Yin et al., 2004; Yin et al., 2005). This observed intra-striatal functional heterogeneity has been interpreted as evidence for a shift in control of behavior from associative to sensorimotor corticostriatal loops as habits develop (Yin and Knowlton, 2006).

It is not currently known whether the pattern of localization observed in the rodent striatum is preserved in the human brain, as ethical concerns limit experimentation and naturally occurring striatal damage such as that resulting from Parkinson's disease is not sufficiently precise. Therefore, to assess the degree to which the subregional specificity for habits present in rodents is also present in the human, we conducted a coordinates-based meta-analytic review of human fMRI experiments reporting putative habit-related activation across a variety of tasks. Tasks included in the review are as follows: probabilistic classification, maze navigation,

instrumental learning with outcome devaluation, sequential decision making, and motor sequence learning. We focus specifically on experiments in 1) healthy human subjects that 2) report habit-related activation of the dorsal striatum (caudate, putamen, or both caudate and putamen). Findings for each of the five tasks are discussed separately below, and peak voxel locations are projected onto a 3D rendering of the dorsal striatum in Fig. 4.1.

Materials and Methods

Studies included in the meta-analysis were identified through extensive review of the literature via a combination of database searches and consultation of review articles. First, we searched PsycINFO and Web of Science for peer-reviewed articles published in English using the following search terms: ("habit" OR "habits" OR "probabilistic classification" OR "weather prediction" OR "response learning" OR "instrumental conditioning" OR "instrumental learning" OR "reinforcement learning" OR "outcome devaluation") AND ("basal ganglia" OR "caudate" OR "putamen" OR "striatum") AND ("fMRI" OR "functional magnetic resonance imaging" OR "functional MRI"). We then checked the reference sections of major review papers, searched for articles written by major contributors to the field, and consulted major contributors to the field to identify additional studies.

Next, studies were reviewed for inclusion using the following criteria. First, the study had to report original fMRI data using healthy human subjects. Studies that were conducted with clinical populations or older adult samples were included only if data from a control group were published in the article or in supplementary materials accompanying the article. Second, studies were included only if they reported habit-related activation of the dorsal striatum (caudate, putamen, or both). We included both studies that used whole-brain analyses and studies that used region of interest analyses, notating for each study the approach that was used. Third, studies

included in the meta-analysis employed one of the following tasks: probabilistic classification, maze navigation, instrumental learning with outcome devaluation, sequential decision making (limited to studies estimating contributions of model-based versus model-free learning), or motor sequence learning (limited to studies contrasting late versus early learning).

This procedure yielded a total of 24 papers. These papers were coded for number of subjects, the habit manipulation(s) or measure(s) used, the contrast(s) used in the imaging analysis, the reported subregion(s) of activation (caudate, putamen, or both), and the coordinates of peak voxels, if reported. Coordinates reported in Talairach space were converted to Montreal Neurological Institute space using GingerALE 2.3.6.

Results

Probabilistic Classification

fMRI studies of probabilistic classification comprise some of the earliest work on the neural basis of human habit learning. In these experiments, participants are shown visual cues that are probabilistically related to outcomes, and they gradually learn the cue-outcome relationships through trial-by-trial feedback. For example, in the weather prediction task, participants are shown a combination of patterned cards and are asked to indicate whether the cards predict sunshine or rain. Relationships between cues and outcomes are not readily apparent to participants performing the task, which discourages use of declarative memory. Patients with limbic-diencephalic amnesia show normal learning on this task in spite of having no declarative memory for the learning episode, whereas patients with Parkinson's disease, which affects striatal function, show impaired learning (Knowlton et al., 1996).

Findings from 11 fMRI studies of probabilistic classification are listed in Table 4.1. Of these, four reported activation of the caudate (Fera et al., 2005; Poldrack et al., 2001; Poldrack et

al., 1999; Weickert et al., 2009), one reported activation of the putamen (Foerde et al., 2006), and six reported activation of both subregions (Aron et al., 2006; Aron et al., 2004; Celone et al., 2011; Schwabe et al., 2013; Schwabe and Wolf, 2012; Seger and Cincotta, 2005). The engagement of both caudate and putamen is consistent with the hypothesis that probabilistic classification can be supported by both declarative and habit memory, with task strategies varying across individuals.

Activation peaks reported in these studies of probabilistic classification are shown in Figure 4.1 in red. These activation peaks were located primarily in anterior caudate and anterior putamen. Activation peaks located in posterolateral putamen were from studies that included manipulations intended to increase habitual responding, namely distraction (Foerde et al., 2006) and stress (Schwabe et al., 2013; Schwabe and Wolf, 2012).

Maze Navigation

Tasks involving maze navigation have long been used in the rodent literature to contrast navigation strategies with different neural substrates (Packard et al., 1989; Packard and McGaugh, 1992; Yin and Knowlton, 2004). These studies suggest that navigation based on distal cues and memory for location history is supported by the hippocampus and dorsomedial striatum, whereas navigation based on proximal cues and stimulus-response associations (i.e., navigation on the basis of habits) is supported by the dorsolateral striatum. Researchers have adapted the maze navigation tasks used in rodents for use in humans by employing virtual reality environments that participants can navigate while stationary in an fMRI scanner.

Findings from four fMRI studies of habit-based navigation are listed in Table 4.2. Three of these studies reported activation of the caudate (Banner et al., 2011; Etchamendy et al., 2012; Iaria et al., 2003), although it is important to note that these three studies employed *a priori*

region of interest analyses that included the caudate but did not include the putamen. Such region of interest analyses allow for less stringent correction for multiple comparisons than whole-brain analyses or analyses that use the entire dorsal striatum as a region of interest. Thus, they are a powerful tool for investigating specific hypotheses, but do not afford conclusions about regions that are outside the search volume. A more recent habit-based navigation study employing a region of interest analysis that included both caudate and putamen reported activation of both subregions (Horga et al., 2015). Unlike previous navigation studies that relied on individual differences in navigation strategy, this study correlated brain activity with estimates of model-free learning, a technique described in more detail below in the section on sequential decision tasks.

Activation peaks reported in these studies of maze navigation are shown in Figure 4.1 in green. The caudate activation peaks tended to be located more posteriorly than the activation peaks from studies of probabilistic classification, corresponding to activation in the body and tail of the caudate. Putamen activation peaks from the single study that included the putamen as a region of interest were located in the posterolateral putamen (Horga et al., 2015).

Outcome Devaluation

Another longstanding method for investigating habit behavior in rodents is to train an instrumental response by rewarding the animal for performing it with a desired outcome (e.g., a food pellet), and then devaluing the outcome (e.g., through sensory-specific satiety or taste aversion conditioning). Insensitivity to the devaluation procedure, shown by continued performance of the devalued response, is taken as evidence of habit formation (Dickinson, 1985). Although this procedure is considered the "gold standard" for determining whether a behavior

has become habitual in rodents, there have been relatively few studies demonstrating devaluation insensitivity in humans.

Four studies that have employed this procedure in conjunction with fMRI are listed in Table 4.3. The first of these studies, using the putamen as a region of interest, reported stimulus onset-related putamen activation in a group of participants who developed a devaluation-insensitive response after overtraining (Tricomi et al., 2009). A subsequent study, using a region of interest that included both caudate and putamen, reported putamen activation in people who showed stress-induced devaluation insensitivity when compared to non-stressed, devaluation sensitive controls (Soares et al., 2012). Similarly, in a study on the effects of hydrocortisone and the α2-adrenoceptor antagonist yohimbine on habit behavior, the group that received both drugs showed insensitivity to devaluation, demonstrating that pharmacological stress can also create devaluation-insensitive responding (Schwabe et al., 2012). Using a region of interest that included both caudate and putamen, this study reported that across participants, activation of the putamen was modulated by salivary α-amylase, an indicator of adrenergic activity.

Finally, in a recent paper that employed a novel instrumental learning task designed to rapidly induce habitual responding, activation of the caudate during early learning correlated with subsequent devaluation insensitivity (Liljeholm et al., 2015). This study included both caudate and putamen as regions of interest but notably did not observe a relationship between activation of the putamen during early learning and subsequent devaluation insensitivity. Although further research is necessary to confirm this hypothesis, it is possible that the correspondence between activation in the caudate during early learning and insensitivity to devaluation indicates that the caudate may support the early learning of behaviors that will later become habitual, while the putamen may support the execution of well-trained habit behaviors.

Activation peaks reported in these studies of outcome devaluation are shown in Figure 4.1 in orange. The activation peaks were all located posteriorly, in either the posterior half of putamen or the tail of the caudate.

Sequential Decision Making

In the computational neuroscience literature, a distinction has been made between "model-free learning," posited as being akin to stimulus-response habit behavior, and "model-based learning," posited as being akin to goal-directed behavior (Daw et al., 2005). The fundamental difference between these two learning systems is that the model-based learner makes decisions using an internal model of the environment, whereas the model-free learner relies on a strategy of repeating rewarded behaviors. Based on this framework, a number of studies have attempted to describe these systems and how arbitration between them is accomplished (for review, see Dolan and Dayan, 2013; Doll et al., 2012). One approach has been to use a sequential decision task in combination with computational modeling to determine the extent to which a subject's behavior is under model-free versus model-based control (Daw et al., 2011; Glascher et al., 2010). Consistent with the idea that model-free learning involves habitual or automatic processes, this procedure has been used to show that acute stress and performance of a secondary task can decrease model-based contributions to learning while leaving model-free contributions intact (Otto et al., 2013a; Otto et al., 2013b).

In conjunction with fMRI, sequential decision making tasks can be used to identify brain regions whose activity correlates with estimated internal subject variables specific to each controller. Initial investigations using this approach only identified activation related to model-free control in the ventral striatum (Daw et al., 2011; Glascher et al., 2010), but two subsequent studies reported activation related to model-free control in the dorsal striatum as well (Doll et al.,

2015; Lee et al., 2014). Findings from these two studies are listed in Table 4.4. Both studies found model-free prediction error signals in the putamen that that survived whole brain correction. Furthermore, model-free *Q*-signals were found with a region of interest analysis in the putamen (Lee et al., 2014), and across participants, putamen prediction error activation was found to correlate with model-free choice (Doll et al., 2015).

Activation peaks reported in these studies of sequential decision making are shown in Figure 4.1 in yellow. These activation peaks were found in lateral putamen throughout the anterior-posterior axis.

Motor Sequence Learning

Motor sequence learning has traditionally been considered to be a different type of procedural learning than habit learning, but recent reviews on habit behavior (Daw and O'Doherty, 2014; Wood and Rünger, 2016) have pointed out that several motor sequence learning studies have reported practice-related increases in activation of the dorsal striatum. Three such studies are listed in Table 4.5. All of these studies reported increases in activation of the putamen as the motor sequence was practiced (Fernández-Seara et al., 2009; Lehéricy et al., 2005; Steele and Penhune, 2010).

Activation peaks reported in these studies of motor sequence learning are shown in Figure 4.1 in blue. Two peaks were located in posterolateral putamen (Fernández-Seara et al., 2009; Lehéricy et al., 2005) and one was located in the putamen more anteriorly (Steele and Penhune, 2010).

Discussion

This review of putative habit-related fMRI activation in the human dorsal striatum (caudate and putamen) found that there do appear to be task-related differences in the

distribution of activations. Specifically, studies using probabilistic classification tasks tended to report either activation of the caudate or of both caudate and putamen, and peak voxels tended to be located in the anterior portion of these structures. In contrast, studies using maze navigation tasks tended to report activation in the caudate that was located more posteriorly, in the body and tail of the caudate. Finally, studies using outcome devaluation, sequential decision making, and motor sequence learning tasks most frequently reported activation in the lateral putamen.

One goal of this project was to evaluate the evidence that the subregional specificity for habits in the rodent dorsal striatum is conserved across species. In the rodent, the dorsolateral striatum appears to subserve habits, while the dorsomedial striatum appears to subserve goal-directed behavior (Yin and Knowlton, 2004; Yin and Knowlton, 2006; Yin et al., 2004; Yin et al., 2005). Conservation across species, therefore, would predict habit-related activation in the human putamen (analogous to the rodent dorsolateral striatum), and in our meta-analysis we observed that findings from studies using outcome devaluation, sequential decision making, and motor sequence learning tasks were generally consistent with this hypothesis.

Outcome devaluation procedures are the strongest test of habitual behavior, and therefore studies that employ outcome devaluation are of special interest. Three out of the four reviewed studies using this method reported activation in the putamen. The other two tasks that were found to yield habit-related activation of the putamen, the sequential decision task and the motor sequence learning task, represent relatively recent conceptualizations of habit and will require further research to determine whether they generate signals that are fundamentally similar to signals found using outcome devaluation or whether they capture different aspects of habit behavior. One issue that remains to be resolved is that an agent with complete insensitivity to devaluation would not be expected to continue to show the sort of model-free prediction error

signaling that has been detected in the putamen using the sequential decision task, as this signaling is based on computation of expected rewards and detection of deviations from these expected rewards. One hypothesis is that the putamen generates model-free prediction error signals during the early stages of habit formation, but that such signaling would decrease with overtraining and be replaced by a simple response to stimuli historically associated with reward regardless of their current value.

In contrast to studies using outcome devaluation, sequential decision, and motor sequence learning tasks, we found that studies using probabilistic classification and maze navigation tasks often reported activation of the caudate. It is possible, therefore, that these two tasks are relatively less well-suited for the study of habit behavior in humans, and that fMRI studies using these tasks contain signals of both goal-directed and habit-based control. Further evidence for this interpretation comes from the fact that of the probabilistic classification and maze navigation studies we reviewed, the ones that reported more lateral activations included manipulations that would increase habit responding (i.e., stress and distraction), or used estimates of model-free learning similar to those used in studies of sequential decision making. One direction for future research would be to combine outcome devaluation procedures with these tasks in humans as has been done in the rodent with maze navigation (Sage and Knowlton, 2000). This would provide more direct confirmation of habit responding, and would allow researchers to eliminate or group separately participants who fail to develop devaluation insensitivity.

Finally, a surprising number of studies reviewed used region of interest analyses that did not include both dorsal striatal subregions. This makes it difficult to draw firm conclusions about subregional specificity, as the level of activation in the voxels not included in the region of interest is not known. Given the variety of findings from studies of putative habit learning, we

recommend that the entire dorsal striatum be used as a region of interest, or, if this is not possible due to lack of power, that region of interest analyses include partial coverage of each subregion (e.g., by using spherical regions of interest centered on coordinates from previous studies such as those included in this review). This will help clarify the individual contributions of the caudate and putamen to habit behavior.

Acknowledgments

The authors thank Wendy Wood and Pei-Ying Lin for comments on this project and for directing us to additional studies.

Tables and Figures

Table 4.1

Locations of dorsal striatal activations reported by studies using probabilistic classification learning tasks

Paper	*N*	Habit Manipulation/Measure	Contrast	Activation
Poldrack et al., 1999	8	Probabilistic feedback	Task > control (perceptual-motor)	caudate
Poldrack et al., 2001	13	Probabilistic feedback	Task > control (perceptual-motor)	caudate
Ibid.	13, 13	Probabilistic feedback	Task > control (paired associate)	caudate
Ibid.	13	Probabilistic feedback	Activation modulated by task experience	caudate
Ibid.	14	Probabilistic feedback	Task > baseline	caudate
Ibid.	14	Probabilistic feedback	Activation modulated by task experience	caudate
Aron et al., 2004	15	Probabilistic feedback	Task > baseline	caudate, putamen
Fera et al., 2005	18	Probabilistic feedback	Task > control (perceptual-motor)	caudate
Ibid.	18	Probabilistic feedback	Activation modulated by performance (accuracy)	caudate
Ibid.	18	Probabilistic feedback	Activation modulated by performance (latency)	caudate
Seger & Cincotta, 2005	15	Probabilistic feedback	Task > baseline	caudate, putamen
Ibid.	15	Probabilistic feedback	Activation modulated by performance (accuracy)	caudate
Aron et al., 2006	8	Probabilistic feedback	Task > control (perceptual-motor)	caudate, putamen
Ibid.	8	Probabilistic feedback	Task > control (perceptual-motor)	caudate, putamen
Foerde et al., 2006	14	Probabilistic feedback, distraction	Activation modulated by performance (accuracy)	putamen
Weickert et al., 2009	25	Probabilistic feedback	Task > control (perceptual-motor)	caudate
Celone et al., 2011	19	Probabilistic feedback	Task > control (perceptual-motor)	caudate, putamen
Schwabe & Wolf, 2012	30	Probabilistic feedback	Task > control (perceptual-motor)	caudate, putamen
Ibid.	30	Probabilistic feedback, stress	Task > control (perceptual-motor)	caudate, putamen
Ibid.	30	Probabilistic feedback, stress	Activation modulated by performance (accuracy)	caudate, putamen
Schwabe et al., 2013	75	Probabilistic feedback, stress	Task > control (perceptual-motor)	caudate, putamen
Ibid.	19	Probabilistic feedback, stress	Activation modulated by performance (accuracy)	caudate

Table 4.2

Locations of dorsal striatal activations reported by studies using maze navigation tasks

Paper	*N*	Habit Manipulation/Measure	Contrast	Activation
Iaria et al., 2003	7	Non-spatial strategy use	Task > control (perceptual-motor)	caudate
Ibid.	7	Non-spatial strategy use	Activation modulated by performance (accuracy)	caudate
Ibid.	7	Non-spatial strategy use	Activation modulated by performance (latency)	caudate
Banner et al., 2011	5, 16	BDNF polymorphism Met allele	Met > Val, training	caudate
Ibid.	5, 16	BDNF polymorphism Met allele	Met > Val, probe test	caudate
Etchamendy et al., 2012	23	Memory inflexibility (continuous)	Activation modulated by flexibility, training	caudate
Ibid.	15	Memory inflexibility (subgroup)	Task > control (perceptual-motor), probe test	caudate
Horga et al., 2015	54	Model-free learning estimates	Prediction error signal, all subjects	caudate
Ibid.	54	Model-free learning estimates	*Q*-signal, all subjects	caudate, putamen
Ibid.	15	Model-free learning estimates	*Q*-signal, learners	putamen
Ibid.	15, 39	Model-free learning estimates	*Q*-signal, learners > non-learners	caudate, putamen

Table 4.3

Locations of dorsal striatal activations reported by studies using outcome devaluation tasks

Paper	*N*	Habit Manipulation/Measure	Contrast	Activation
Tricomi et al., 2009	15	Overtraining	Late > early	putamen
Soares et al., 2012	12, 12	Stress	Stress > control	putamen
Schwabe et al., 2012	69	Pharmacological stress	Activation modulated by α-amylase level	putamen
Liljeholm et al., 2015	19	Devaluation insensitivity	Activation modulated by devaluation insensitivity	caudate

Table 4.4

Locations of dorsal striatal activations reported by studies using sequential decision making tasks

Paper	*N*	Habit Manipulation/Measure	Contrast	Activation
Lee et al., 2014	22	Model-free learning estimates	Prediction error signal	putamen
Ibid.	22	Model-free learning estimates	*Q*-signal	putamen
Doll et al., 2015	20	Model-free learning estimates	Prediction error signal	putamen
Ibid.	20	Model-free learning estimates	Activation modulated by model-free choice	putamen

Table 4.5

Locations of dorsal striatal activations reported by studies using motor sequence learning tasks

Paper	*N*	Habit Manipulation/Measure	Contrast	Activation
Lehéricy et al., 2005	14	Overtraining	Activation modulated by task experience	putamen
Fernández-Seara et al., 2009	14	Overtraining	Late > early	putamen
Steele & Penhune, 2010	15	Overtraining	Late > early	putamen

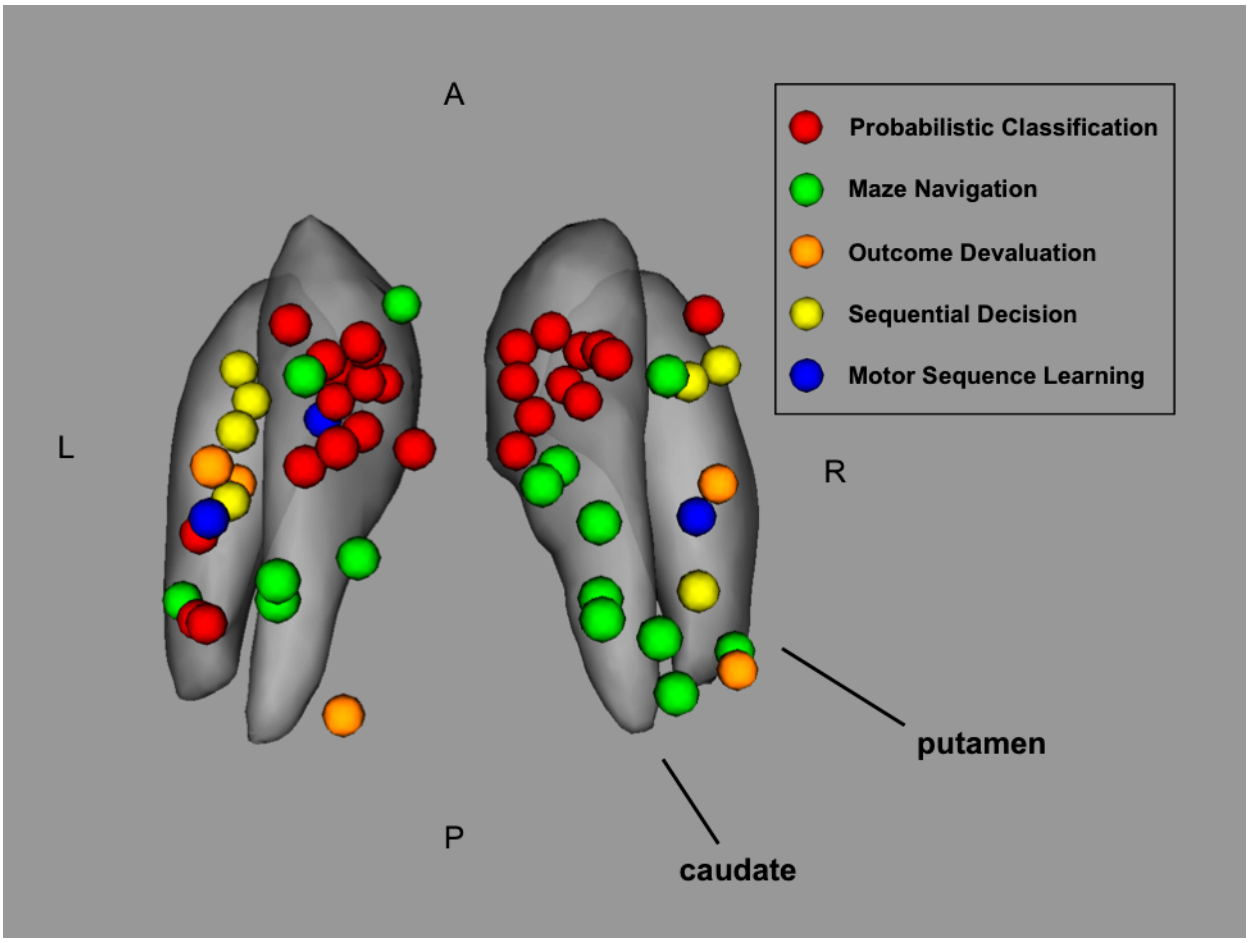

Figure 4.1. Peak coordinate locations from fMRI studies of habit behavior by task. Coordinates of peak voxel activation reported in the studies listed in tables 4.1 – 4.5 are projected onto a 3D rendering of caudate and putamen (axial view). Coordinates reported in Talairach space were converted to Montreal Neurological Institute space using GingerALE 2.3.6. For studies using probabilistic classification tasks (red), activations clustered around anterior caudate and anterior putamen. Activations from maze navigation studies (green) tended to occur more posteriorly in the body and tail of the caudate. Peak voxels from studies of outcome devaluation (orange), sequential decision making (yellow), and motor sequence learning (blue) were located in the lateral putamen. A, anterior; P, posterior; L, left; R, right.

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CHAPTER 5

Concluding Remarks

This series of studies provides evidence in support of the hypothesis that the habit learning system that has been described in non-human animals has several features that appear to be conserved in the human, and that early-life stress (ELS) has lasting effects on this system. Specifically, Study 1 and Study 2 demonstrated that ELS increases habit behavior of young adults, in line with research in rodents showing a similar pattern (Grissom et al., 2012). In Study 1, we showed that there are striking similarities between the pattern of partial reinforcement extinction behavior obtained in rodents with hippocampal lesions and humans with a history of ELS, and we proposed a multiple memory systems perspective that explains these findings as evidence of increased habit responding resulting from impaired declarative memory.

In Study 2, we modified a recently developed shock avoidance procedure (Gillan et al., 2014) by replacing shocks with aversive noises, and showed that people who reported a history of ELS were more likely to continue making a trained response to stimuli that had been selectively devalued. Devaluation insensitivity is a fundamental part of habit responding in animals, yet it has been difficult to observe in humans. Our research contributes to the growing evidence that using aversive stimuli may be a fruitful avenue of research toward this end.

In Study 3, we assessed the current fMRI literature on habit behavior to evaluate the hypothesis that the human putamen plays a similar role to the rodent dorsolateral striatum in habitual responding (Yin and Knowlton, 2006). Results from studies using outcome devaluation, sequential decision, and motor sequence learning tasks were consistent with this hypothesis, whereas results from studies using probabilistic classification and maze navigation tasks were

not. It is possible that the lack of consistent activation of the putamen during the performance of probabilistic classification and maze navigation tasks indicates that these tasks are not as well-suited for the study of habit behavior in humans.

As discussed in Chapter 1, a growing number of experiments have demonstrated that stress increases habitual responding (e.g., Kim et al., 2001; Schwabe et al., 2008; Schwabe et al., 2007). In the rodent, there is evidence that the behavioral shifts toward habit responding after stress are accompanied by specific neural changes: selection of a stimulus-response habit strategy by chronically stressed mice is associated with decreased hippocampal neurogenesis (Ferragud et al., 2010), and rats exposed to chronic stress that produces outcome devaluation insensitivity show atrophy of brain regions that support goal-directed behavior and hypertrophy of brain regions that support habit behavior (Dias-Ferreira et al., 2009). These findings, in combination with evidence indicating that stress that occurs early in development can have effects on the habit behavior of the organism at a later developmental stage (Grissom et al., 2012; Schwabe et al., 2012), led us to hypothesize that ELS may become neurally embedded in the systems that support instrumental behavior, and may thereby affect responding long after the stress experienced during development is no longer present.

A possible process by which this may occur is shown in Figure 5.1. Stress that occurs during development may result in underactivity of structures supporting declarative memory and goal-directed behavior (hippocampus, prefrontal cortex, caudate) and compensatory overactivity of structures supporting habit behavior (sensorimotor cortex, putamen). Ultimately this could result in an overreliance on habit responding, putting people with a history of ELS at risk of premature death due to negative health behaviors such as substance abuse and overeating. The fact that people with a history of ELS have increased risk of premature death that can be

attributed to negative health behaviors is undeniable (Anda et al., 2008; Anda et al., 2006; Dong et al., 2003; Dong et al., 2004; Felitti et al., 1998; Hillis et al., 2000); what is not yet known are the specific neural and behavioral vulnerabilities that lead to these outcomes. Studies 1 and 2 provide evidence that young adults with a history of ELS show increased reliance on habit responding in both appetitive and avoidance habit learning situations, respectively, suggesting that both positive and negative reinforcement may contribute to the development of negative health behaviors in this population. Study 3 provides support for the hypothesis that the putamen supports habitual behaviors such as devaluation insensitive responding in humans, suggesting this area is a potential region of interest for future studies investigating the effects of ELS on the brain. We would predict functional and possibly structural differences in this region of the brain in people with a history of ELS compared to people without. Specifically, we would predict increased activation during instrumental learning, increased connectivity with sensorimotor cortex, and hypertrophy.

In general, it will be important for future habit studies to focus on the temporal aspects of habit formation, both across the development of specific habitual behaviors and across the lifespans of individuals. Some open questions are: how is the switch from goal-directed to habitual control over behavior accomplished, and can it be reversed? Are the neural systems that support appetitive habit formation the same as the ones that support avoidance habit formation? How does the duration of ELS affect future habit behavior? And finally, can the apparent enhanced habit behavior observed in people with a history of ELS be prevented or stopped? Possible directions for prevention and intervention research include the development of stimulus-elicited redirection toward goals, incorporation of mindful awareness and meditation practices, and use of instrumental learning theory to encourage formation of healthy habits.

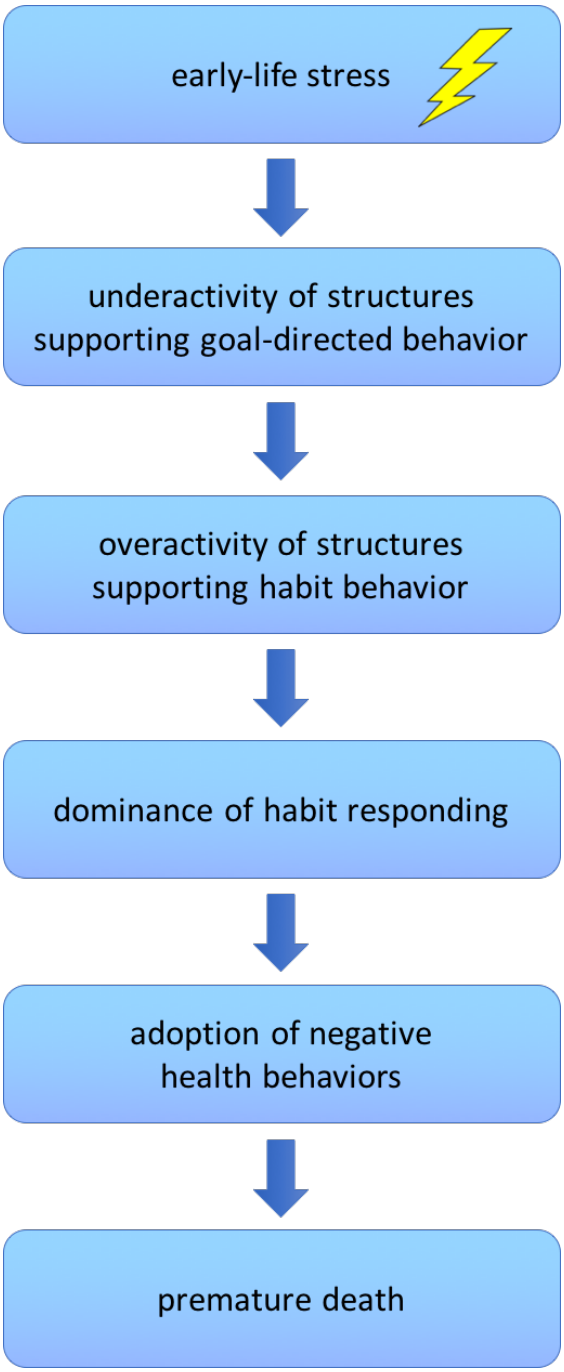

Figure 5.1. Potential process by which early-life stress leads to negative health behaviors and premature death.

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