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Effects of Early-Life Stress on Probabilistic Reversal Learning and Response Perseverance in Young Adults

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Abstract

Early life stress (ELS), including experiences with abuse and neglect, are related to several negative health outcomes in adulthood. One area that has received attention is the increased rate of substance abuse disorder in individuals who had experienced ELS. Given the critical role habitual behavior in the development of substance abuse, ELS may affect the trajectory of neural development such that habitual responding is more dominant than in individuals who did not experience ELS. Here, we examine learning of a probabilistic classification task (the Weather Prediction Task) in healthy young adults who reported significant ELS and those that did not. This task can be learned in a declarative, model-based manner, or in a more habitual, stimulusresponse manner. Participants learned to choose the outcome (sun or rain) that was probabilistically associated with each cue combination through reinforcement on each trial. After 100 trials, the probabilities were reversed, and we conceptualized habitual behavior as perseverating responses based on the old probabilities. We also collected information about subjective socio-economic status (sSES), anxiety, depression, and substance use from participants. Using multiple regression, we found that , we found that our measure of habitual responding was correlated with reported alcohol use, suggesting that our measure of habit has validity for health behaviors. Furthermore, we found that some forms of early life stress led to greater response perseverance after contingencies were reversed. Overall, the results suggest that childhood adversity may contribute to the development of habit.

Keywords

Habit; Learning; Early-life stress; Human; reversal learning

Introduction

Early life stress (ELS; e.g. childhood abuse and neglect) has been linked to a variety of negative physical and psychological health outcomes, including increased risk of substance use disorders (Anda et al., 2002; Dube et al., 2002; Hughes et al., 2017; Sinha &

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Jastreboff, 2013), heart disease (Dong et al., 2004), and early mortality (Kelly-Irving et al., 2013). Previous studies (Anda et al., 2002; Gordon et al., 2020; Lee et al., 2020) have also found significantly higher levels of depression, state/trait anxiety, and current stress among individuals with high compared to low ELS, as well as potentiation of or positive correlations with anxiety and depressive symptoms among individuals experiencing acute stress (Barber et al., 2014; Bogdan & Pizzagalli, 2006; Grillon et al., 2007). Researchers have posited that the link between stress and these negative health outcomes, in particular substance use disorders, is due to differences in striatal-based learning and decision-making processes in non-stressed versus stress-exposed individuals.

Previous studies have found differences in learning and behavioral control among individuals with greater ELS and chronic stress exposure compared to non-stressed controls (Gordon et al., 2020; Hanson et al., 2017; Harms et al., 2018; Patterson et al., 2019; Soares et al., 2012; Wilkinson et al., 2021). For instance, researchers have shown that individuals with greater ELS exposure exhibit slower and less accurate instrumental (stimulus-response-outcome) learning and lower probabilistic learning over time compared to non- or low-exposed peers (Hanson et al., 2017; Harms et al., 2018). Deficits in cognitive flexibility, manifesting as difficulty updating contingencies during reversal learning, alongside reduced positive feedback sensitivity were also found among individuals exposed to ELS (Hanson et al., 2017; Harms et al., 2018; Wilkinson et al., 2021). ELS and chronic stress exposure have also been shown to promote appetitive and aversive habitual responding (Dickinson, 1985; Gordon et al., 2020; Patterson et al., 2019; Soares et al., 2012; Yin & Knowlton, 2006; Zhou et al., 2020). In addition, acute stress exposure has been shown to reduce reward responsiveness/sensitivity, impair aversive reversal learning, and promote habitual responding in human samples (Berghorst et al., 2013; Bogdan & Pizzagalli, 2006; Raio et al., 2017; Schwabe & Wolf, 2009, 2010; Smeets et al., 2019). Thus, we see patterns of contingency learning deficits and difficulty in successfully updating behavior manifest in populations experiencing acute or early life stress.

These deficits may arise due to a stress-related reliance on inflexible sensorimotor (stimulus-response [S-R], habitual) as opposed to dynamic associative (action-outcome [A-O], goal-directed) behavioral response strategies (Soares et al., 2012; Yin & Knowlton, 2006). Previous studies have shown various neurobiological effects of stress exposure, including dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis which governs bodily homeostasis and stress responding; subsequent glucocorticoid/corticosteroid release; alterations in frontal region activation necessary for the updating of environmental associations; and morphological changes in brain regions subserving S-R and associative behavioral control (e.g. frontal and associative striatal atrophy, sensorimotor striatal hypertrophy; Soares et al., 2012; Arnsten, 2009; Raio et al., 2017). A combination of these and other factors (e.g., cognitive load, attention, instrumental and associative learning conditions) likely push behavioral control and decision-making strategies in favor of automatic S-R habit-like processes as opposed to declarative goal-directed behaviors in the face of acute and early life stressors.

Interestingly, the conjunctive effects of both ELS and acute stress on S-R-based learning and behavioral control processes have not been examined. Given that ELS exposure dysregulates

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stress responding, in turn affecting cognitive processes, exposure to acute stress could lead to differential behavioral response patterns in high versus low ELS exposed individuals. In particular, dysregulated stress responding may lead to increased difficulties in learning important environmental contingencies and flexibly updating behavioral responses in high ELS populations, which may be exacerbated under stress or threat. This propensity could explain increased susceptibility among individuals with high ELS in developing substance use disorders, depressive symptoms, and other negative neuropsychological and physical outcomes that are accentuated by other acute and chronic stressors.

To address these gaps in the literature, we had young adults randomly assigned into stress and control groups complete an online modified version of the Weather Prediction Task (WPT; Knowlton et al., 1994) employing a reversal phase to acquire measures of probabilistic reversal learning and response perseverance. Probabilistic classification tasks like the WPT have previously been used to measure different striatal-based learning processes. The WPT presents individuals with probabilistically related cue information to encourage implicit, incremental stimulus-response association acquisition. Studies utilizing the WPT among neuropsychological patients (Eldridge et al., 2002; Knowlton et al., 1994; Knowlton et al., 1996; Sage et al., 2003) support the assertion that performance in the WPT does not require medial temporal lobe structures for declarative memory but can be supported by alternative procedural systems. Using fMRI in healthy young participants, Foerde et al (2006) showed that performance in the WPT was associated with medial temporal lobe or striatal activation depending on task conditions. Here we assess the extent to which learning is more flexible or habitual by including a reversal phase after initial learning of the WPT contingencies to probe flexible learning of new contingencies and initial contingency response perseverance.

Through this study, we aimed to (1) examine the conjunctive effects of ELS and acute stress on probabilistic reversal learning and response perseverance controlling for other influential variables and (2) determine if response perseverance moderates the relationships between ELS and substance use. We predicted similar initial learning performance regardless of ELS or stress exposure as has been previously reported in probabilistic learning paradigms (Schwabe & Wolf, 2012; Wilkinson et al., 2021), but worse performance adjustment (lower accuracy during the reversed compared to the initial probability phase) and increased response perseverance after contingency reversal among the high ELS and stress exposed groups, controlling for measures of depression, anxiety, and perceived SES. We also predicted that response perseverance would moderate the relationships between ELS and substance use outcomes. In addition to total ELS exposure, we examined whether different childhood stressors, including different types of abuse and neglect, differentially impact cognitive flexibility and perseveration. Previous work (Gordon et al., 2020) suggested that early-life neglect may be specifically related to habitual performance on an avoidance learning task.

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Methods

Participants

102 participants (20.56 ± 2.14 years old, range = 18 – 31) were recruited from the University of California, Los Angeles (UCLA) undergraduate psychology subject pool. Eight participants were excluded due to missing data, 3 were excluded due to refusal to continue participation, and 1 was excluded due to technical errors (n = 12). The final sample consisted of 90 participants (20.47 ± 1.90 years old, range = 18 – 28; 64 women, 26 men), with 51 participants in the control group and 39 participants in the stress group. Participants provided verbal informed consent and received credit toward partial completion of a course requirement for participation. All procedures received approval from the UCLA Institutional Review Board.

Modified Weather Prediction Task

To measure probabilistic reversal performance and response perseverance, participants completed a modified online version of the WPT. This version of the WPT was composed of an initial probability phase and a reversed probability phase. During the initial probability phase, participants were visually presented with 100 randomized trials composed of a combination of 1, 2, or 3 card cues, with each card cue combination related probabilistically to a 'rain' or 'sun' weather outcome (see Table 1). Participants were tasked with responding via keyboard which of the two weather outcomes, 'rain' or 'sun', they believed a given combination predicted, with 'rain' corresponding to the 'q' key and 'sun' corresponding to the 'p' key.

After each trial, participants were given answer feedback in order to attach value to each of the combinations, wherein participants were shown a happy or sad face, "Correct!" or "Incorrect!" black text, a description of what the correct prediction had been for the combination (e.g. "the card(s) predicted: rain"), and a score bar accompanied by a "+1" or "−1" if their answers were correct or incorrect, respectively (see Figure 1). The reversed probability phase was similar to the initial probability phase, with one exception: the probabilistic outcomes associated with each card combination were reversed (e.g., combination which initially predicted majority 'rain' outcomes now predicted majority 'sun' outcomes and vice versa; see Table 1). Participants completed 200 trials total (100 trials/probability phase). The task was self-paced, with each trial remaining on screen until a response was given, after which feedback was presented for 2000 ms followed by a 500 ms ISI which consisted of a blank screen. Participant key responses were acquired for all trials.

Trier Social Stress Test Online

To induce acute stress in participants, an online version of the Trier Social Stress Test (TSST) adapted from Gunnar et al. (2021) was utilized. The TSST is a well-studied paradigm for experimental stress induction, and typically includes videorecorded speech and mental math tasks completed in front of a panel of judges to introduce socioevaluative stress effects. During this version of the TSST, a group composed of three experimenters were assigned to one of three roles: Experimenter, Judge 1, and Judge 2. The Experimenter guided the participant throughout the course of the experiment, which was completed using

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the popular cloud-based video conferencing platform Zoom (https://zoom.us/), except when the participant was undergoing the judging portion of the TSST. Judges 1 and 2 were placed in a separate breakout room (a feature available on the Zoom platform wherein individuals can enter a separate "space"/session allowing for privacy from the main Zoom session) in which they administered the stress manipulation, maintaining stoic and clinical personas as is typical of TSST paradigms. Importantly, due to COVID restrictions at the time of experimentation, saliva samples to assess cortisol response could not be taken and were instead replaced with self-report measures to assess stress perception among participants. Moreover, while attempts were made to test participants at consistent timepoints to control for circadian rhythm/time of day effects on the stress (cortisol) response (Kudielka & Wüst, 2010), multiple factors including differences in time zones and participant motivation likely influenced stress induction.

During the TSST, participants watched a calming video (approx. 5 minutes) presented by an experimenter via the "share screen" function on Zoom, after which they completed a self-report measure for stress (State-Trait Anxiety Inventory [STAI] Form). Participants were then moved into a breakout room where two judges awaited them and immediately began recording the session utilizing the Zoom recording feature (employing the local recording option to save the session recording on one of the judge's computers), after which they presented participants with instructions for the speech portion of the TSST. Participants were told they would be evaluated based on their performance and given five minutes to prepare a speech for which they were given the following prompt:

"Imagine that you are in a new class with about 20 other students and that your professor asked you to stand in front of the class and introduce yourself. Talk about yourself, your personality, and why you would be liked by the other students in class. You should talk about at least one good thing and one bad thing about yourself."

During this preparation time, the judges turned off their cameras and muted themselves to provide a sense of privacy for the participant. After the five minutes were over, the judges turned their cameras back on and instructed the participant to give their speech for five minutes, during which they prompted participants to remain on task given any lapses. For instance, if a participant paused for too long or asked how much time was left for the speech portion, one of the judges would prompt them to continue and let them know that their time was not yet up. After the speech portion concluded, participants were instructed to quickly and accurately complete the mental math portion of the TSST (e.g. subtract by 13s starting from the number 938) for five minutes, the parameters of which were adjusted depending on the ease or difficulty of the original prompt (e.g., subtract by 17s, 7s, 3s instead depending on participant performance). Participants were again prompted to remain on task and asked to restart the task given any lapses. Once finished, participants were moved back to the main Zoom session with the initial experimenter and once more completed the self-report measure of stress before going on to complete the WPT. Importantly, any recordings taken of the participants were immediately destroyed after the conclusion of the study session as per the IRB protocol.

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A control version of the TSST, adapted online employing recommendations from Het et al. (2009), was also utilized to compare to the acute stress condition. During the control TSST, participants first watched the same calming video as previously described, after which they completed the self-reported stress/anxiety questionnaire. Participants were then placed in a breakout room by themselves, during which a single experimenter tasked them with thinking about a speech topic, giving a speech on any topic they desired, and then completing an easy mental math exercise (e.g., add 15 starting from 0; 5 minutes/activity, 15 minutes total). The experimenter only entered this breakout room to inform the participant of the instructions for each section and to alert them when each portion had concluded; otherwise, the experimenter remained in the main session. Once participants finished every portion of the control TSST, the experimenter moved them back to the main session where they completed the stress self-report measure once more, after which they moved on to complete the WPT. Participants were not recorded during the placebo TSST.

Questionnaires

Participants completed a demographics form for sample characterization purposes. Participants also completed the Childhood Trauma Questionnaire (CTQ)/Early Experiences Questionnaire-Short Form, a 28-item assessment used to assess levels of ELS. The CTQ consists of 5 subscales which were also used to assess differential effects of different forms of ELS on probabilistic reversal performance and response perseverance: physical abuse (PA), physical neglect (PN), emotional abuse (EA), emotional neglect (EN), and sexual abuse (SA). Participants were also presented with two additional questions assessing exposure to general intrafamilial abuse. Each item was scored on a scale of 1 to 2, 3, or 5, with a minimum of 30 and maximum of 150 relating to lowest to highest ELS exposure, respectively.

To assess depressive symptoms, participants completed the Beck Depression Inventory (BDI), a 20-item assessment with a minimum of 0 and maximum of 60 relating to no or high levels of depressive symptoms, respectively. To assess state and trait anxiety, participants completed the State Trait Anxiety Forms Y1 and Y2 (STAI Forms Y1, Y2), both of which are 20-item questionnaires which assess levels of current and general experiences of anxiety or stress. The STAI Y-1 (state anxiety) was used to assess levels of stress a maximum of 3 times through the course of the experiment. To assess perceived SES, participants completed the MacArthur Scale of Subjective Social Status, a single-item questionnaire which assesses an individual’s perceived socioeconomic standing. Finally, participants completed the Health Behaviors Questionnaire, a 30-item assessment which evaluates alcohol and drug use behaviors, among other health characteristics. In particular, the alcohol use assessment evaluated frequency of risky alcohol use, with scores ranging from 0 (no risky alcohol use) to 36 (high risk of addictive alcohol use). The drug use assessment evaluated frequency of drug use, ranging from 0 to >10 times, in the past 12 months, and measured usage of substances including marijuana, cocaine, heroin, downers, stimulants, hallucinogens, etc.

Procedure

Participants were randomly assigned to the control or stress TSST conditions prior to participation. After joining their experiment session via Zoom (link provided after sign-

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up), experimenters guided the participants in optimizing their Zoom settings and chosen experimental environment (e.g. having the participant utilize gallery mode, move any pets or other distractors in the room with them, or place their phones away from themselves) to ensure a common and less distracting experience across all participants involved in the study.

Upon completing the TSST or control procedure, participants then completed the online modified WPT on their personal computing devices while being monitored by researchers via Zoom to increase task attentiveness and provide additional explanation of task instructions should the participant require it. Participants filled out the stress self-report measure prior to and after TSST or control procedure exposure, and again after completion of the WPT. Following the WPT, participants also completed a demographics form and multiple questionnaires (detailed above). Afterward, participants were debriefed on study procedures.

Data Analysis

All data were analyzed using R (R Core Team, 2020). Importantly, all variables without a meaningful zero were mean centered for regression analyses. For all analyses, unless otherwise noted, a significance level of 0.05 was utilized and standard errors were reported. The experimental group variable (control vs. stress) was dummy coded in all relevant analyses (0 = control, 1 = stress). All linear regression analyses included BDI, trait anxiety, and subjective SES scores as covariates unless otherwise stated. Notably, one individual was again removed from all drug use analyses due to a reported drug use score greater than 3 standard deviations from the mean (score = 11.88).

To determine performance across the different probability phases of the WPT, percent accuracy was acquired for the initial and reversed phases, after which reversal and initial phase accuracy were subtracted from each other to calculate a measure of reversal phase (flexible) performance adjustment, termed the phase accuracy subtraction measure. Scores closer to 0 indicate comparable performance across the initial and reversed probability phases, with positive scores indicating greater reversal phase accuracy and negative scores indicating greater initial phase accuracy. Lower scores indicate poor learning of the new contingencies, corrected for initial performance level.

To determine perseverance of initial contingency responding, otherwise termed response perseverance, participant responses during the reversed probability trials were coded as adhering to initial probabilistic majority responses (1) or not (0). For example, if a card combination during the initial probability phase predicted ‘rain’ on 80% and ‘sun’ on 20% of this combination’s presentations, this combination was considered a majority ‘rain’ probability trial; participants who continued to make ‘rain’ responses during the reversed probability phase, despite the reversal of this probabilistic relationship, were thus classified as having continued reliance on initial probabilities despite the devaluation of these relationships (1), and thus perseverating in their responses, or not (0). The average proportion of these responses was then calculated for each individual and multiplied by 100 to create a percent response perseverance score, with higher scores indicating a higher

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percentage of response perseverance. A high score on this measure indicates maintenance of the original contingencies during performance.

Results

Sample characteristics are reported in Table 2 separated by experimental group and gender. Welch *t*-tests indicated that control and stress groups exhibited similar levels of overall and subtype ELS, depression, trait anxiety, subjective SES, alcohol use, and drug use scores (*ps* > 0.263).

To characterize relationships between ELS and mood, perceived SES, and substance use outcomes, five Bonferroni-corrected correlations ($\alpha = 0.01$) were conducted between ELS and BDI (depression) scores, trait anxiety, subjective SES, alcohol use, and drug use. Results revealed that ELS scores significantly positively correlated with BDI scores (r = 0.432, $p < 0.001$, 95% CI [0.247, 0.586]) and trait anxiety scores (r = 0.496, $p < 0.001$, 95% CI [0.322, 0.638]), indicating that ELS relates to higher depression and trait anxiety expression among young adults. No other correlations were significant (*ps* > 0.049).

To assess whether online TSST exposure successfully induced stress among experimental participants, an ELS (low, high) x Experimental Group (control, stress) x Time (1, 2, 3) mixed factorial ANOVA was conducted on state anxiety scores (see Figure 2). Results revealed significant main effects of Experimental Group ($F(1, 86) = 5.921$, $p = 0.017$, generalized $\eta^2 = 0.041$) and Time ($F(2, 172) = 37.947$, $p < 0.001$, generalized $\eta^2 = 0.143$) qualified by a significant Experimental Group x Time interaction ($F(2, 172) = 6.807$, $p = 0.001$, generalized $\eta^2 = 0.029$). Tukey-corrected post-hoc comparisons revealed no difference in state anxiety scores between the control (37.5 ± 1.38) and stress groups (39.5 ± 1.60) before TSST exposure ($t(86) = -0.945$, $p = 0.933$) but significantly greater state anxiety scores in the stress group (49.7 ± 1.51) compared to the control group (41.0 ± 1.31) after TSST exposure ($t(86) = -4.327$, $p < 0.001$), though this difference did not persist after completion of the behavioral task ($t(86) = -0.605$, $p = 0.990$; stress = 48.4 ± 1.58. control = 47.1 ± 1.37). For the stress group, post-hoc tests also showed significantly greater state anxiety scores for time points 2 (after TSST exposure; $t(86) = -6.055$, $p < 0.001$) and 3 (after behavioral testing; $t(86) = -4.764$, $p < 0.001$) compared to baseline, with no difference in state anxiety scores between time points 2 and 3 ($t(86) = 0.923$, $p = 0.940$). For the control group, post-hoc tests also showed no difference in stress scores between baseline and time point 2 (after TSST exposure; $t(86) = -2.426$, $p = 0.159$), but interestingly indicated significantly greater stress scores for time point 3 (after behavioral testing) compared to time point 2 ($t(86) = -4.934$, $p < 0.001$) and baseline ($t(86) = -5.946$, $p < 0.001$). ELS did not affect state anxiety nor did it interact with other variables (*ps* > 0.110).

To examine effects of ELS, experimental group condition, and probability phase on accuracy, the continuous ELS measure was dichotomized into low versus high ELS exposure via median split. The low ELS group reported they “Never” or “Rarely” experienced any of the stressors on the CTQ (ELS: 39.86 ± 5.06, range = 30 – 47). In contrast, the high ELS group reported experiencing stressors on the CTQ at least “Sometimes” during childhood

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(ELS: 64.67 ± 15.51, range = 48 – 113). A mixed factorial ANOVA was conducted on accuracy using probability phase as a within-subjects variable and dichotomized ELS and experimental group condition as between-subjects variables. Results for the Probability Phase (initial, reversed) x ELS (low, high) x Experimental Group (control, stress) mixed factorial ANOVA revealed a significant main effect of Probability Phase ($F(1, 86) = 55.761$, $p < 0.001$, generalized $\eta^2 = 0.206$) qualified by a significant Probability Phase x ELS interaction ($F(1, 86) = 4.672$, $p = 0.033$, generalized $\eta^2 = 0.021$; see Figure 3). Post-hoc tests revealed significantly greater accuracy for the high ELS (65.2 ± 1.32%) compared to the low ELS group (60.7 ± 1.43%) during the initial probability phase ($t(86) = 2.310$, $p = 0.023$), but no difference in accuracy between the two groups during the reversed phase ($t(86) = -0.302$, $p = 0.763$; high ELS = 54.0 ± 1.16%, low ELS = 54.6 ± 1.26%). Results also revealed a significant ELS x Experimental Group interaction ($F(1, 86) = 5.350$, $p = 0.023$, generalized $\eta^2 = 0.036$). Post-hoc tests indicated no difference in overall task accuracy between high (57.6 ± 1.30%) and low ELS groups (58.9 ± 1.33%) in the control group ($t(86) = -0.697$, $p = 0.488$), but significantly greater accuracy for the high ELS (61.6 ± 1.41) compared to the low ELS group (56.4 ± 1.61) in the stress condition ($t(86) = 2.458$, $p = 0.016$). No other effects were significant (*ps* > 0.165).

To determine if ELS and stress exposure affected reversal phase performance adjustment, a multiple linear regression was conducted using the phase accuracy subtraction measure as the dependent variable and ELS, experimental group condition (control or stress), and their interaction as predictors. Results revealed no significant effects (*ps* > 0.051). Because previous studies had shown differential effects of ELS subscales on cognitive variables (e.g., Gordon et al., 2020), another multiple linear regression was conducted utilizing all five ELS subscales (PA, PN, EA, EN, SA) and experimental group condition as predictors. Interactions between the ELS subscales and experimental group condition were not included due to non-significance of the interaction term in the original model and concerns of overfitting. Results revealed a significant negative effect of childhood sexual abuse (b = −1.586, $p = 0.016$) and a significant positive effect of BDI scores (b = 0.394, $p = 0.031$) on predicted reversal phase performance adjustment. This indicates that, holding all other terms constant at their means, for every unit increase in sexual abuse exposure, we observe a decrease in accuracy adjustment after the reversal of 1.59%, and for every unit increase in BDI scores, we observe a 0.39% increase in the accuracy subtraction measure. No other terms were significant (*ps* > 0.116; see Table 3 and Figures 4A and 4B for partial regression plots).

As in phase accuracy adjustment, to determine if ELS and stress exposure affected response perseverance, a multiple linear regression was conducted using the response perseverance measure as the dependent variable and ELS, experimental group condition (control or stress), and their interaction as predictors. Results revealed no significant effects (*ps* > 0.069). Another multiple linear regression was conducted using similar terms alongside the ELS subscales to determine their differential effects on response perseverance. Results revealed significant positive effects of emotional neglect exposure (b = 0.694, $p = 0.040$), sexual abuse exposure (b = 0.964, $p = 0.042$), and subjective SES (b = 1.381, $p = 0.017$) as well as a significant negative effect of emotional abuse exposure (b = −0.533, $p = 0.041$) on

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response perseverance. No other terms were significant (*ps* > 0.166; see Table 4 and Figures 5A, 5B, 5C, and 5D for partial regression plots).

To assess effects of ELS, stress exposure, and reversal phase performance adjustment or response perseverance on reported alcohol and drug use frequency behaviors, four linear regressions were conducted using either reported frequency of alcohol or drug use as the dependent variable and the ELS subscales, experimental group condition, and the reversal phase performance adjustment or response perseverance measures as predictors. Results for the phase accuracy subtraction model showed a significant positive effect of childhood physical neglect exposure on alcohol use (b = 0.352, *p* = 0.047; see Figure 6A for a partial regression plot), but no other significant terms for this model (*ps* > 0.242; see Table 5) or the drug use model (*ps* > 0.132). Results for the response perseverance models also revealed significant positive effects of physical neglect exposure (b = 0.415, *p* = 0.014) and response perseverance (b = 0.168, *p* = 0.003) on alcohol use (see Table 6 and Figures 6B and 6C for partial regression plots). No other terms were significant in the alcohol use (*ps* > 0.226) or the drug use models (*ps* > 0.050).

Notably, due to potential effects of gender on stress and psychological variables, all analyses were repeated including gender as a covariate. No main effects of gender nor significant gender interactions were found for stress scores over time (*ps* > 0.149) or task accuracy (*ps* > 0.059). When included in the multiple linear regression analyses, gender was also not a significant predictor of reversal phase performance adjustment (overall ELS model: *p* = 0.232, ELS subscale model: *p* = 0.333), response perseverance (overall ELS model: *p* = 0.218, ELS subscale model: *p* = 0.550), alcohol use (reversal phase performance adjustment model: *p* = 0.471, response perseverance model: *p* = 0.516), or drug use (reversal phase performance adjustment model: *p* = 0.397, response perseverance model: *p* = 0.400). We conclude that gender did not exert any significant influence on the pattern of results noted here.

Discussion

This study examined the conjunctive effects of ELS and acute stress exposure on probabilistic reversal learning and response perseverance, aiming to extend previous work on the effects of stress on learning and behavioral control (Gordon et al., 2020; Patterson et al., 2019; Schwabe & Wolf, 2012; Wilkinson et al., 2021). Somewhat in line with predictions, and in accordance with previous studies (Gordon et al., 2020; Mundy et al., 2015), we found significant positive relationships between ELS and depressive symptoms and trait anxiety, indicating susceptibility to psychological disorders among individuals with greater early life stress exposure. In addition, we observed significantly greater increases in subjective stress for individuals in the stress condition compared to the control condition, providing further validation for the online version of the TSST (Gunnar et al., 2021) as a method of stress induction. In our probabilistic reversal learning task, we found significantly greater accuracy among the high ELS compared to the low ELS group during the initial probability phase. In contrast to predictions, the acute stress manipulation led to greater accuracy among the high compared to low ELS group in both the initial and reversal phases. As predicted, we found a significant negative effect of childhood sexual abuse exposure on

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reversal phase performance adjustment controlling for other covariates, indicating deficits in reversal adjustment due to ELS. Childhood emotional neglect, sexual abuse, and subjective SES reports were associated with significant increases in perseverative responses, while emotional abuse exposure was associated with a reduction in response perseverance, indicating differential effects of ELS subtypes on stimulus-response behaviors. Lastly, we found significant positive effects of physical neglect exposure and response perseverance on alcohol use, indicating that some types of ELS exposure alongside habit-like behavioral control may predict substance use.

The findings in the present study coincide with a vast literature showing the negative effects of ELS exposure on psychological and health outcomes. We replicated findings showing susceptibility to depressive symptomology (Chapman et al., 2004), trait anxiety (Mundy et al., 2015), and alcohol use among individuals who underwent adverse childhood experiences. Our sample consisted of university students which included many participants with little reported early life stress and relatively modest levels of drug and alcohol use. It is highly likely that additional effects of ELS would emerge in a larger sample with greater exposure to ELS and more reported substance use. Thus, we do not interpret our null results. Nevertheless, the fact that even in this resilient and healthy sample, relationships emerged between reported ELS, alcohol consumption, perseveration, and cognitive flexibility on our laboratory task is noteworthy. This study was also successful in replicating socioevaluative stress effects from the Gunnar et al. (2021) online-adapted version of the TSST. Nevertheless, we acknowledge that the lack of cortisol measurement and other physiological data limited our ability to make inferences about how changes in endocrine responses (e.g., relating to the activation of the HPA axis stress response) may also have impacted the current findings. Moreover, results from the validation of the TSST-OL (Gunnar et al., 2021) also indicated lower psychobiological stress responding compared to an in-vivo version of the TSST, which may have impacted the effectiveness of stress induction in the current study. Future work may benefit from a replication of the observed results using endocrine and other physiological measures of stress as well as in person TSST exposure.

Interestingly, our findings concerning greater accuracy among the high ELS exposure group during the initial probability phase and overall in the high ELS-stress group were not predicted. Previous studies have shown differences in task strategy, response time, learning rate, and stimulus discrimination during probabilistic learning among ELS or acute stress exposed groups compared to controls, but no differences in task accuracy (Schwabe & Wolf, 2012; Wilkinson et al., 2021). It has been noted that employment of probabilistic reversal paradigms and exposure to stress, whether in early life or acute, generate a reliance on striatal systems that subserve S-R learning and suppression of hippocampus-dependent memory systems (Knowlton et al., 1994; Patterson et al., 2013; Schwabe et al., 2009). Thus, these results may reflect advantages among stress exposed groups, who already rely on S-R and other striatal-dependent strategies during probabilistic learning, over non-stressed groups whose reliance on hippocampal-based explicit learning strategies may not be as effective for this task.

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Importantly, we found deficits in reversal performance adjustment and promotion of response perseverance among individuals with higher compared to lower ELS exposure, in line with predictions and extant literature (Gordon et al., 2020; Harms et al., 2018; Patterson et al., 2019; Zhou et al., 2020). Childhood sexual abuse exposure was a significant predictor of both measures, indicating difficulties among individuals who experienced this specific type of ELS in flexibly adapting associations and responses to novel contingencies. Exposure to childhood sexual abuse has been associated with dysregulation of the HPA axis (de Bellis et al., 1994); prevalence of psychopathology, including greater incidence of depression, anxiety, and PTSD (Adams et al., 2018); and susceptibility to development of substance use disorders, including alcohol and drug dependencies (Fletcher, 2021; Hayatbakhsh et al., 2009; Skinner et al., 2016). Similarly, childhood emotional neglect has also been shown to relate to increased risk of depression and anxiety (Salokangas et al., 2020; Spertus et al., 2003) and substance use (Schimmenti, et al., 2022). Many of these detrimental outcomes have been shown or theorized to be related to deficits in behavioral flexibility and perseverative phenotypes, which were explored in this study. Thus, we provide evidence that exposure to these childhood stressors promotes a reliance on perseverative response strategies and difficulties with adapting to new environmental contingencies. This association may then exacerbate, derive from, or influence the development of some negative health consequences attributed to childhood stressors, in particular psychological and substance use disorders.

However, despite various findings showing that acute stress attenuates reversal learning (Raio et al., 2017) and promotes inflexible and perseverative behavioral response strategies (Schwabe & Wolf, 2010; Smeets et al., 2019), we did not see any effects of TSST exposure on reversal adjustment nor response perseverance. We also did not observe significant interactions between ELS and acute stress exposure on these variables. This is surprising due to expectations that the dysregulation of physiological stress responding observed in high ELS samples would lead to exacerbation of cognitive deficits, including behavioral control and flexibility, when such populations were under stress; that is, given both types of stress promote reliance on S-R habit-like processes, in part due to the physiological impacts of stress, we posited an additive influence of these stressors on cognitive processes. We thus expected to see worse probabilistic accuracy, larger differences in initial versus reversed learning, and even greater promotion of perseverative responding in the stressed high ELS group compared to low ELS and control samples, which were not observed. Given that this study was completed online at the height of the SARS-CoV-2 pandemic, it may be the case that 1) our online stress manipulation was not sufficient in effecting change in behavioral responding and/or 2) stress responding and reactivity were affected by current circumstances. Another related possibility is that performing the WPT task was sufficiently stressful such that the TSST procedure did not substantially increase stress levels. Findings from one study also suggest that stress exposure *per se* is not responsible for difficulties with behavioral flexibility, but rather stress-induced cortisol reactivity (Smeets et al., 2019), which was not acquired in the current study. Future in-person replications of this work collecting neuroendocrine and physiological stress measures would aid in parsing out acute stress effects on probabilistic reversal learning and response perseverance.

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This study also found separate significant effects of ELS and response perseverance on alcohol use, reflecting the potential validity of utilizing laboratory-derived behavioral flexibility measures to predict substance use issues, whose link has been posited by numerous researchers (Schwabe et al., 2011, but see Vandaele & Ahmed, 2020, and Hogarth, 2020). ELS has consistently been shown to correlate with or predict substance use issues, as we have replicated here, but researchers have posited a moderating or mediating effect of behavioral inflexibility on ELS-substance use relationships. Some researchers have explored these relationships using self-reported flexibility (Odacı et al., 2021), but such measurements are subject to differences in metacognitive ability, do not provide multidimensional assessments of behavioral flexibility, and may not correlate with laboratory-derived measures of behavioral control. Thus, we expand on this literature by showing that individual differences in S-R based perseverative responding, reflecting a type of cognitive inflexibility, can predict risky alcohol use in a young adult, non-clinical sample regardless of ELS exposure. However, we cannot ignore the possibility that long-term subclinical substance use contributes to individual differences in behavioral control and perseverative responding, or that ELS and associated neuropsychological factors alter behavioral control and substance use behaviors in distinct manners. Future studies using representative clinical samples would help illuminate the directionality of these ELS-behavioral control-substance use relationships.

Conclusion

In this examination of the effects of early life and acute stress exposure on probabilistic reversal learning and response perseverance, we found that certain types of ELS including childhood sexual abuse related to greater initial accuracy, poorer probabilistic reversal adjustment, and increased response perseverance among a young adult sample. Moreover, we found that childhood physical neglect exposure and response perseverance positively predicted alcohol use, reflecting poorer substance use outcomes among individuals exposed to specific early life stressors and those who have increased individual propensity toward behavioral inflexibility. These findings suggest that laboratory measures of cognitive flexibility may be sensitive to substance use behavior.

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- Individuals who report experiencing early-life stress demonstrate greater perseveration when contingencies were reversed in a probabilistic classification task
- Sexual abuse and emotional neglect during childhood showed the most robust association with reduced cognitive flexibility.
- Perseveration after reversal in the probabilistic classification task was associated with greater alcohol consumption.

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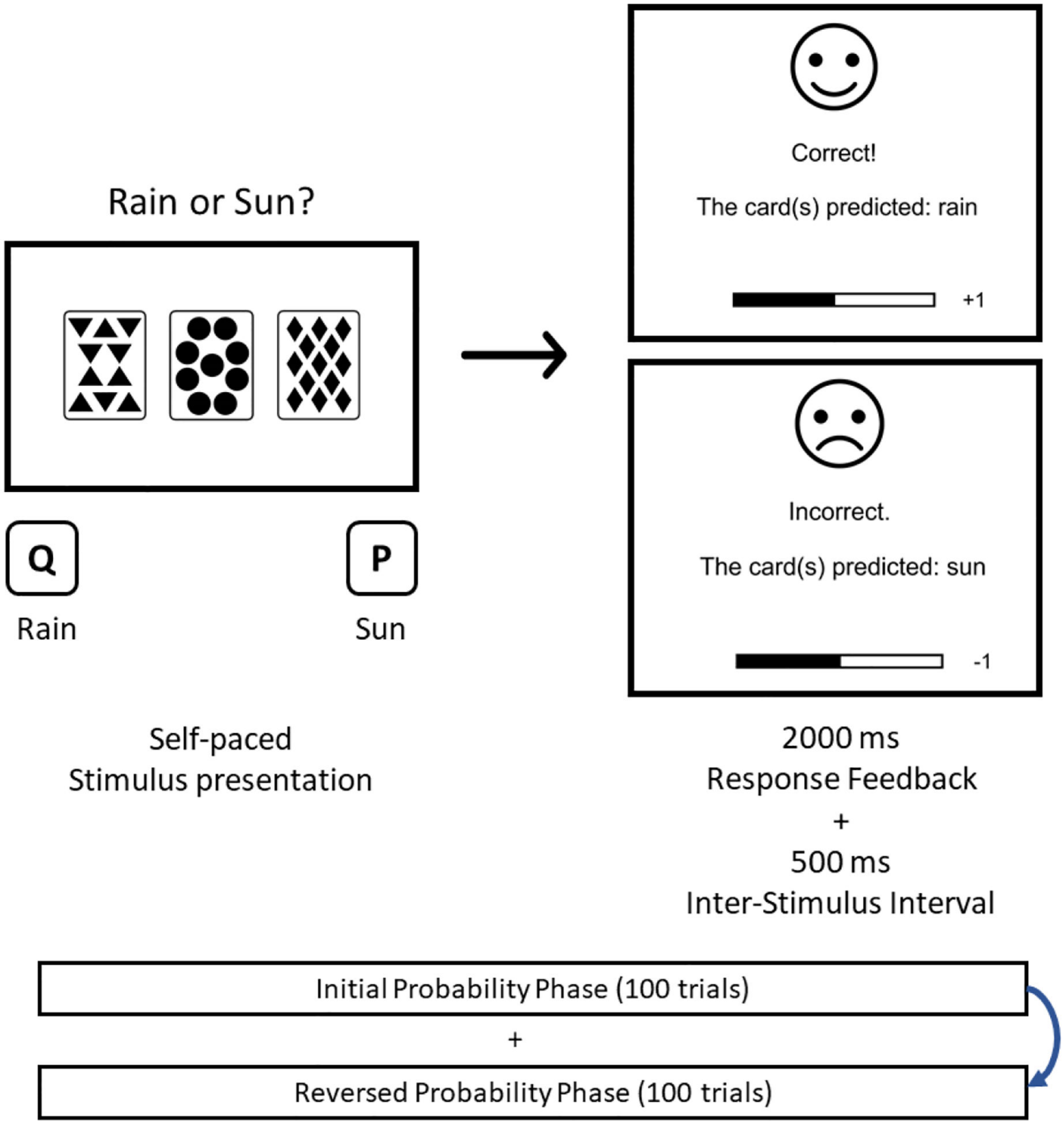

Figure 1. Task schematic.

Participants were tasked with viewing card combination stimuli and predicting the associated weather outcomes (rain, ‘q’; sun, ‘p’). Participants received either positive or negative feedback depending on response accuracy. Unbeknownst to participants, the card stimuli held probabilistic associations with the weather outcomes which were later switched during a probabilistic reversal phase (100 trials/probability phase, 200 trials total).

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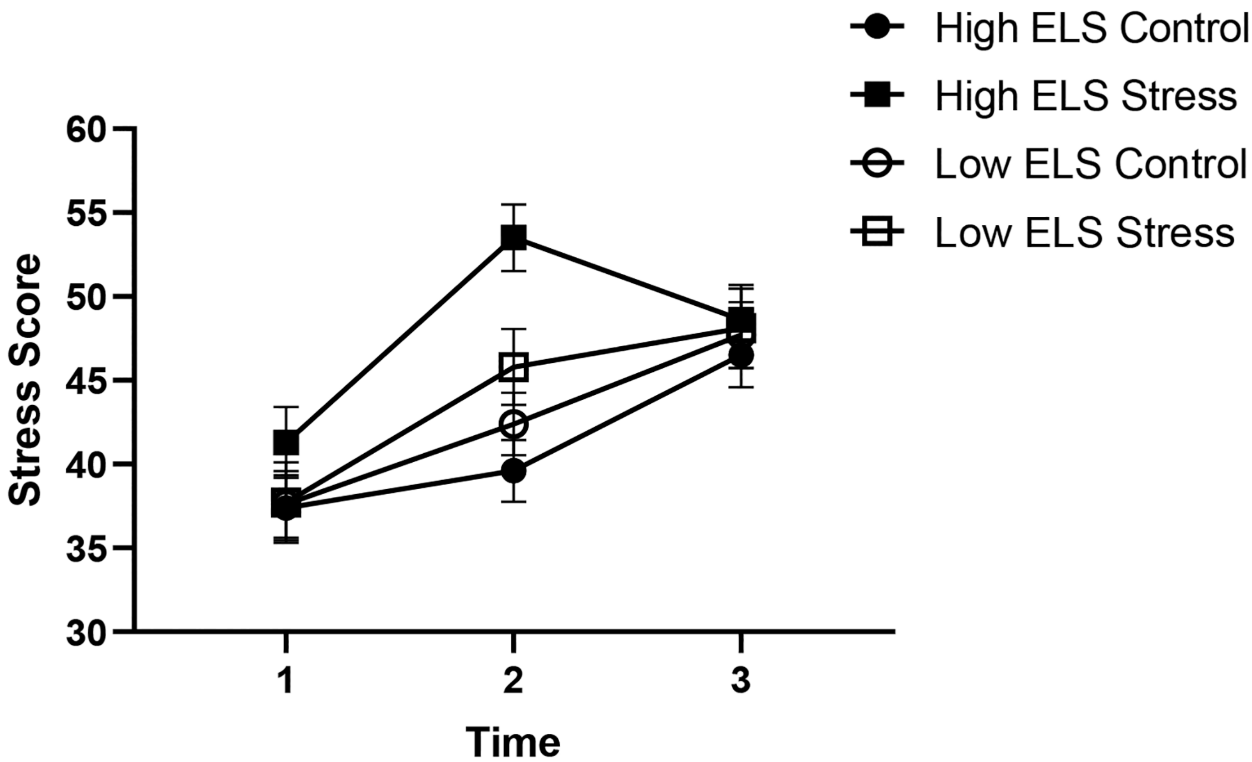

Figure 2. Experimental group differences in self-reported stress.

Stress scores over the experimental time course separated by ELS and experimental group. Error bars denote standard error of the means.

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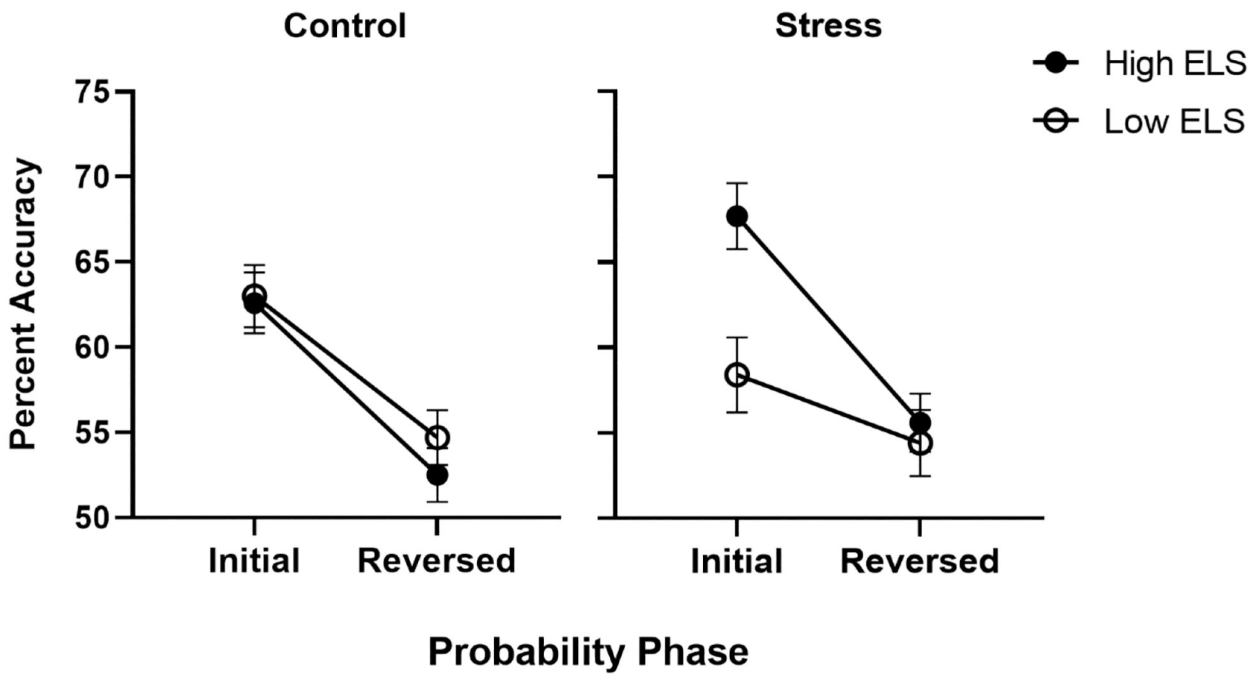
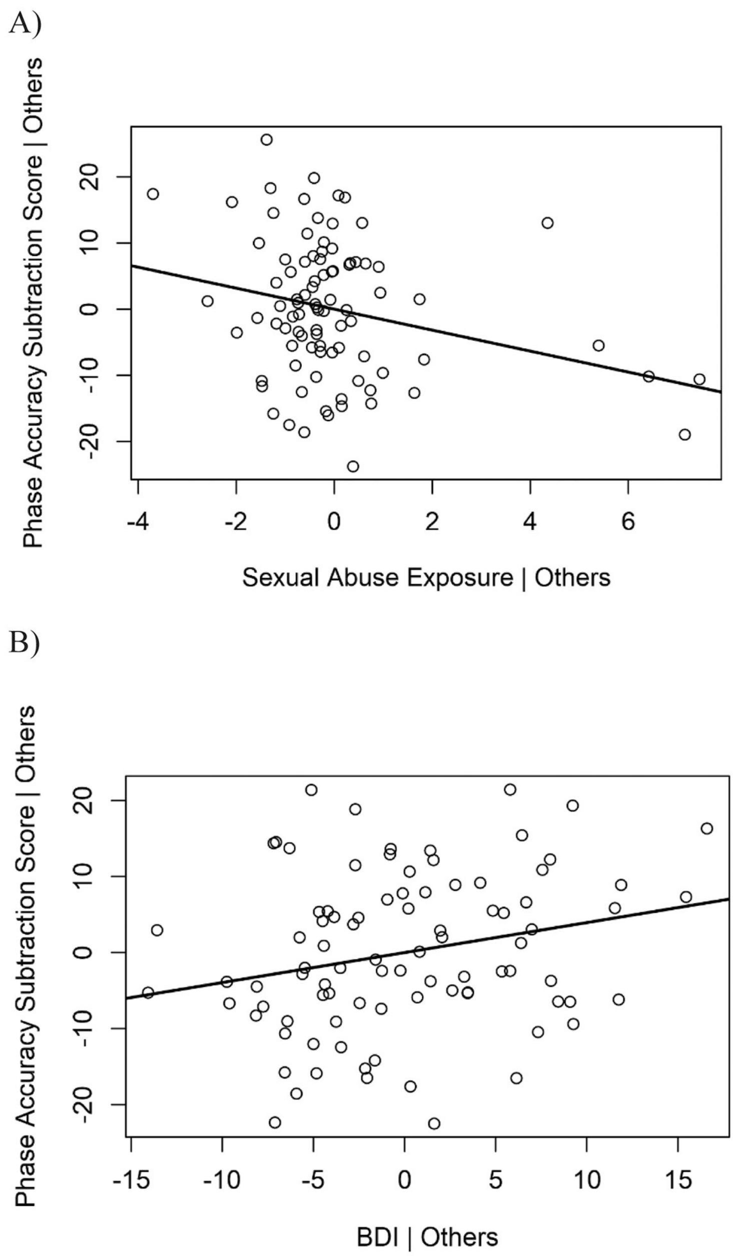


Figure 3. Differences in percent accuracy based on probability phase, ELS group, and experimental condition.

Significantly greater accuracy among the high compared to low ELS group during the initial probability phase and among the high compared to low ELS group in the stress condition. Error bars denote standard error of the means.



Figures 4A and 4B. ELS and depression effects on reversal adjustment.

Partial regression plots showing that childhood sexual abuse exposure (A, top) and depressive symptomology (B, bottom) significantly predict phase accuracy subtraction scores, controlling for other variables at their means.

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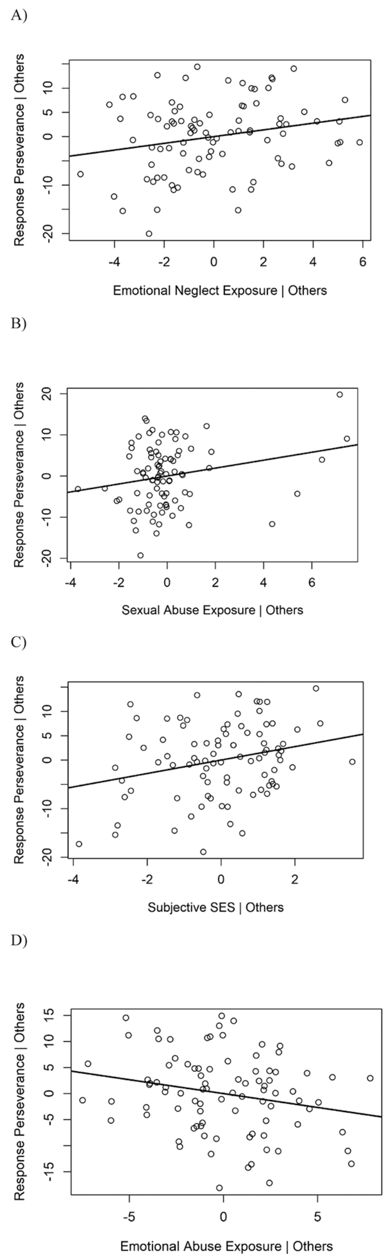

Figures 5A, 5B, 5C, and 5D. ELS and subjective SES effects on response perseverance.
Partial regression plots showing that response perseverance is positively predicted by childhood emotional neglect (A), sexual abuse (B), and subjective SES (C) and negatively predicted by emotional abuse (D), controlling for all other variables at their means.

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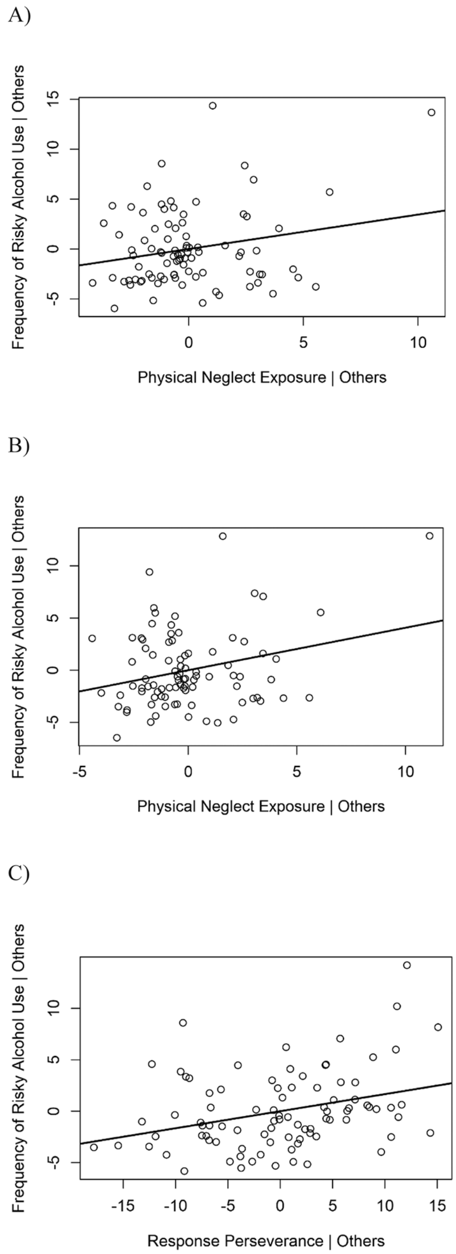

Figures 6A, 6B, and 6C. Effects of childhood physical neglect exposure and response perseverance on frequency of risky alcohol use.

Partial regression plots showing significant positive effects of childhood physical neglect exposure on frequency of risky alcohol use in models accounting for reversal phase performance adjustment (A) or response perseverance (B), among other covariates. Response perseverance also significantly positively predicted alcohol use (C).

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Table 1.

Probabilistic structure of the modified Weather Prediction Task.

Stimuli					All Phases	Initial Probability Phase	Reversed Probability Phase
Pattern	**Cue 1**	**Cue 2**	**Cue 3**	**Cue 4**	**P (pattern)**	**P (rain|pattern)**	**P (rain|pattern)**
A	0	0	0	1	0.14	0.143	0.857
B	0	0	1	0	0.08	0.375	0.625
C	0	0	1	1	0.09	0.111	0.889
D	0	1	0	0	0.08	0.625	0.375
E	0	1	0	1	0.06	0.167	0.833
F	0	1	1	0	0.06	0.5	0.5
G	0	1	1	1	0.04	0.25	0.75
H	1	0	0	0	0.14	0.857	0.143
I	1	0	0	1	0.06	0.5	0.5
J	1	0	1	0	0.06	0.833	0.167
K	1	0	1	1	0.03	0.333	0.667
L	1	1	0	0	0.09	0.889	0.111
M	1	1	0	1	0.03	0.667	0.333
N	1	1	1	0	0.04	0.75	0.25

Note. The presence or absence of card cues within certain patterns will be denoted as 1s or 0s, respectively. The overall probability of rain for each probability phase was 50% (sum of P (pattern) * P (rain|pattern) across all patterns).

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Table 2.

Participant characteristics separated by experimental group and gender.

Variables	**Control (n=51)**	**Stress (n=39)**	**Female (n=64)**	**Male (n=26)**
Overall ELS	52.96 (16.78)	53.26 (17.82)	52.70 (17.19)	54.04 (17.31)
PA	6.76 (3.16)	6.77 (3.26)	6.66 (2.90)	7.04 (3.86)
PN	7.31 (3.10)	7.23 (3.03)	7.00 (3.15)	7.96 (2.73)
EA	11.24 (4.81)	11.03 (5.72)	11.50 (5.27)	10.27 (4.99)
EN	9.73 (4.41)	9.92 (4.09)	9.59 (4.13)	10.35 (4.57)
SA	5.75 (1.78)	6.08 (2.33)	5.83 (1.90)	6.04 (2.36)
BDI	16.08 (9.87)	13.74 (9.63)	15.17 (9.28)	14.81 (11.11)
Trait Anxiety	47.14 (9.51)	47.05 (9.97)	47.59 (9.69)	45.88 (9.65)
Subjective SES	6.04 (1.34)	6.00 (1.78)	5.92 (1.47)	6.28 (1.70)
Alcohol Use	3.45 (4.05)	4.08 (4.18)	3.34 (3.60)	4.65 (5.07)
Drug Use	2.10 (3.92)	1.69 (2.36)	1.77 (2.43)	2.31 (4.92)

Note. Mean (SE) scores on psychological measures grouped by experimental condition (control vs. stress groups) and gender (female, male). Physical Abuse = PA, Physical Neglect = PN, Emotional Abuse = EA, Emotional Neglect = EN, and Sexual Abuse = SA.

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Table 3.

Results from a multiple linear regression showing significant effects of childhood sexual abuse exposure and depressive symptomology on the phase accuracy subtraction measure (bolded), holding all other variables constant at their means.

Variable	Estimate	SE	*t*-value	*p*
Intercept	−9.649	1.506	−6.409	< 0.001
PA	−0.119	0.498	−0.239	0.812
PN	−0.475	0.459	−1.033	0.305
EA	−0.117	0.354	−0.330	0.742
EN	0.153	0.458	0.335	0.739
SA	**−1.586**	**0.642**	**−2.471**	**0.016**
Experimental Group	1.788	2.300	0.777	0.434
BDI	**0.394**	**0.180**	**2.194**	**0.031**
Trait Anxiety	−0.284	0.179	−1.591	0.116
Subjective SES	−0.828	0.782	−1.058	0.293

$R^2 = 0.179$, Adj. $R^2 = 0.085$, $F(9, 79) = 1.908$, $p = 0.063$

Note. SE = standard error. Physical Abuse = PA, Physical Neglect = PN, Emotional Abuse = EA, Emotional Neglect = EN, and Sexual Abuse = SA. Experimental group was dummy coded as 0 (control group) or 1 (stress group).

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Table 4.

Results from a multiple linear regression showing significant effects of childhood emotional abuse, emotional neglect, sexual abuse, and subjective SES on response perseverance (bolded), holding all other variables constant at their means.

Variable	Estimate	SE	*t*-value	*p*
Intercept	46.275	1.094	42.292	< 0.001
PA	0.006	0.362	0.016	0.987
PN	−0.273	0.334	−0.817	0.416
EA	**−0.533**	**0.257**	**−2.073**	**0.041**
EN	**0.694**	**0.333**	**2.085**	**0.040**
SA	**0.964**	**0.466**	**2.067**	**0.042**
Experimental Group	−1.395	1.671	−0.835	0.406
BDI	0.183	0.131	1.398	0.166
Trait Anxiety	−0.044	0.130	−0.343	0.733
Subjective SES	**1.381**	**0.568**	**2.430**	**0.017**

$R^2 = 0.152$, Adj. $R^2 = 0.055$, $F(9, 79) = 1.57$, $p = 0.139$

Note. SE = standard error. Physical Abuse = PA, Physical Neglect = PN, Emotional Abuse = EA, Emotional Neglect = EN, and Sexual Abuse = SA. Experimental group was dummy coded as 0 (control group) or 1 (stress group).

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Table 5.

Results from a multiple linear regression showing a significant effect of childhood physical neglect exposure on reported alcohol use (bolded), holding all other variables constant at their means.

Variable	Estimate	SE	*t*-value	*p*
Intercept	12.981	0.700	18.548	< 0.001
PA	−0.221	0.188	−1.178	0.242
PN	**0.352**	**0.174**	**2.017**	**0.047**
EA	−0.000	0.133	−0.001	0.999
EN	−0.032	0.173	−0.184	0.854
SA	0.307	0.251	1.223	0.225
Experimental Group	0.782	0.870	0.898	0.372
BDI	0.021	0.070	0.295	0.769
Trait Anxiety	0.039	0.068	0.565	0.574
Subjective SES	0.318	0.297	1.071	0.287
Phase Accuracy Sub.	−0.036	0.042	−0.860	0.393

$R^2 = 0.137$, Adj. $R^2 = 0.026$, $F(10, 78) = 1.236$, $p = 0.282$

Note. SE = standard error. Physical Abuse = PA, Physical Neglect = PN, Emotional Abuse = EA, Emotional Neglect = EN, and Sexual Abuse = SA. Experimental group was dummy coded as 0 (control group) or 1 (stress group).

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Table 6.

Results from a multiple linear regression showing significant effects of childhood physical neglect and response perseverance on reported alcohol use (bolded), holding all other variables constant at their means.

Variable	Estimate	SE	*t*-value	*p*
Intercept	5.544	2.623	2.114	0.038
PA	−0.218	0.178	−1.221	0.226
PN	**0.415**	**0.165**	**2.511**	**0.014**
EA	0.094	0.130	0.721	0.473
EN	−0.154	0.169	−0.915	0.363
SA	0.203	0.236	0.859	0.393
Experimental Group	0.951	0.828	1.150	0.254
BDI	−0.025	0.065	−0.376	0.708
Trait Anxiety	0.056	0.064	0.883	0.380
Subjective SES	0.116	0.291	0.399	0.691
Response Perseverance	**0.168**	**0.055**	**3.035**	**0.003**

$R^2 = 0.221$, Adj. $R^2 = 0.121$, $F(10, 78) = 2.208$, $p = 0.026$

Note. SE = standard error. Physical Abuse = PA, Physical Neglect = PN, Emotional Abuse = EA, Emotional Neglect = EN, and Sexual Abuse = SA. Experimental group was dummy coded as 0 (control group) or 1 (stress group).