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The role of early life adversity and inflammation in stress-induced change in reward and risk processes among adolescents

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Abstract

Background: Early life adversity (ELA) has long been associated with increased risk for stress-related psychopathology, particularly depression. The neuroimmune network hypothesis posits that ELA increases sensitivity to psychosocial stress, moderating the association between increases in peripheral markers of inflammation and decreases in reward outcomes linked to anhedonia and risk-taking behaviors. The present study examined this hypothesis in a sample of adolescents by using acute psychosocial stress to probe the role of inflammatory signaling in behavioral measures of reward and risk processing.

Method: 80 adolescents [13.86 years (SD=1.54); 45% female], oversampled for ELA, underwent the Trier Social Stress Test for Children while providing blood samples immediately before and 60-minutes after stress onset. Blood samples were assayed for plasma IL-6. One hour before stress onset, and then 60 minutes after, participants completed computer-administered behavioral tasks measuring reward (Pirate Task) and risk (Balloon Analog Risk Task).

Results: ELA moderated the association between increases in IL-6 and decreases in risk tolerance in pursuit of rewards ($p = .003$) and reward response bias ($p = .04$). Stress-induced increases in IL-6 were associated with decreases in pumps for rewards among adolescents exposed to high, relative to little or no, ELA. Further, greater IL-6 increases were associated with increases in bias toward high relative to low value rewards among adolescents with low adversity exposure but not among those exposed to higher adversity.

Conclusions: The present study provides the first evidence in a pediatric sample that ELA may alter the role of stress-induced inflammation in reward and risk processing, and may extend our understanding of why stress leads to depression in this high-risk population.

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Introduction

Depressive episodes are between three and six times more likely in the month following a stressful life event than months without stressful events (Hammen, 2015, 2005; Kendler et al., 1999). Stressful experiences activate multiple psychophysiological processes that serve short-term goals at the potential expense of long-term goals, which may contribute to the generation of subsequent stressors, further depletion of psychosocial resources, and increased risk for depressive episodes (Hammen, 2006; Uliaszek et al., 2012). A better understanding of individual differences in psychobiological responses to stress may elucidate how stress leads to depression and for whom this putative pathway is clinically relevant.

Stress leads to depression, in part, by altering the neural and psychological underpinnings of reward and promoting anhedonia (Pizzagalli, 2014). Reward is a multifaceted psychological construct that involves both motivation and responsiveness (Rømer Thomsen et al., 2015), which have been conceptualized as “wanting,” “learning,” and “liking” in preclinical models (Berridge et al., 2009). Reward motivation or “wanting” reflects the amount of desire an individual has for any given reward and is often operationalized by the amount of effort that individual is willing to put into attaining rewards and at what cost. Inherent in reward motivation, particularly among adolescents, is the willingness to take on risk in pursuit of rewards. Risk-taking tends to occur among individuals who are more sensitive to rewards and exhibit diminished behavioral control capacity, characteristics typically observed among clinical populations of adolescents relative to adults (Bjork and Pardini, 2015; Geier, 2013; Peeters et al., 2017; van Duijvenvoorde et al., 2016). In contrast, reward-related response bias involves the extent to which an individual learns to associate certain behaviors or cues with rewards and is then cognitively or behaviorally influenced by the value of that reward. Learning in the context of reward is thought to be influenced by the degree of consummatory pleasure or “liking” an individual experienced upon reward receipt. These domains of reward have somewhat distinct underlying neurobiology and clinical implications when dysregulated (Admon and Pizzagalli, 2015; Huys et al., 2013), creating an imperative to distinguish between them in translational research that stands to inform clinical interventions.

Immune activation can induce many features of depression (Dooley et al., 2018), including anhedonia (Eisenberger et al., 2010). Randomized-controlled trials of endotoxin have shown that immune activation decreases positive mood (Reichenberg et al., 2001), decreases appetite, and increases anhedonia as measured by ventral striatum responses to reward (Eisenberger et al., 2010). A small number of human studies using exogenous activation of the immune system have corroborated these observations with more objective behavioral tasks designed to distinguish between domains of reward processing. Increases in IL-6 following experimental endotoxemia have been associated with both exaggerated (Lasselin et al., 2016) and attenuated reward motivation (Draper et al., 2018), while IL-6 reactivity following the influenza vaccine was associated with a decrease in reward motivation (Boyle et al., 2019). Studies examining reward responsiveness are also equivocal, with two studies using a mild inflammatory challenge showing that IL-6 reactivity increases reward responsiveness (Boyle et al., 2020, 2019) and one endotoxin study showing no effect of IL-6

reactivity on reward responsiveness (Draper et al., 2018). Together, these findings suggest that while inflammatory activity modulates reward processes, the direction of those effects vary by reward subdomain or the magnitude of inflammatory reactivity.

Psychosocial stress also reliably activates the innate immune system (Segerstrom and Miller, 2004; Slavich and Irwin, 2014; Steptoe et al., 2007). Yet, only one study to date has examined the effects of stress-induced inflammation on any aspect of reward motivation and none have examined risk. In this isolated study IL-6 reactivity was associated with an increase in reward motivation, even when the probability of reward was low (Boyle et al., 2020). Garnering a clearer understanding of these processes in the context of psychosocial stress is essential given the epidemiological links between stress and depression (Hammen, 2015, 2005; Kendler et al., 1999). The existing literature has also exclusively examined the effects of inflammatory activity on reward processes in adult populations. Understanding the role of neuroimmune communication in the link between stress and depression during adolescence is critical to reducing the burden of depression and other stress-related diseases on individuals and society. Psychobiological sensitivity to stress is one such pathway. Adolescence is a period of increased sensitivity to social stressors (Blakemore, 2008; Fuhrmann et al., 2015), in part because a hallmark of adolescence is a re-orientation of social cognition away from an individual's family of origin and toward peers (Burnett and Blakemore, 2009). Adolescence is also when markers of chronic low-grade inflammation first emerge among populations at high risk for the development of depression, namely early life adversity (ELA)-exposed youth (Kuhlman et al., 2020a).

The impact of immune activation on reward processing may be altered among individuals exposed to ELA. ELA comprises diverse childhood experiences such as living in poverty, loss of or separation from parents, maltreatment, or having a caregiver with a mental illness (Felitti et al., 1998). The neuroimmune network hypothesis posits that ELA increases communication between the central nervous and immune systems in ways that presage stress-related diseases, in part, by attenuating reward processes (Nusslock and Miller, 2015). Characterizing this potential mechanism is developmentally and clinically relevant because ELA is one of the most robust risk factors for depression (Green et al., 2010; Kessler et al., 2010c; McLaughlin et al., 2010, 2012), potentially through these effects on reward. The vast majority of evidence for variation in neuroimmune communication as a function of ELA comes from preclinical experiments in rodents (e.g. Bolton et al., 2019; Johnson and Kaffman, 2018; Menard et al., 2017), with very few translations to humans. In one study, young adults exposed to ELA were more susceptible to depressed mood and subjective cognitive complaints following mild immune activation with the annual influenza vaccine (Kuhlman et al., 2020b). Further, in a sample of adolescents, children living in poverty with the greatest ventral striatal reactivity to rewards evidenced the highest systemic inflammation (Miller et al., 2021). Indeed, inflammation and depressive symptoms appear to be more strongly correlated among adolescents exposed to ELA (Miller and Cole, 2012). However, these studies have also largely focused on outcomes which do not distinguish between reward subdomains or explicitly measure risk tolerance.

We have previously shown that adolescents exposed to ELA show exaggerated inflammatory gene expression following exposure to standardized psychosocial stress, but not exaggerated

IL-6 responses (Kuhlman et al., 2022). The present study sought to extend this observation by examining whether ELA also contributes to individual differences in reward following stress-induced inflammation in the same sample, with an explicit focus on characterizing both reward and risk using tasks that have been previously validated for use in pediatric samples. We hypothesized that greater inflammatory reactivity to stress would be associated with greater decreases in risk tolerance in pursuit of rewards and reward response bias for high relative to low-value rewards, and that these associations would be strongest among adolescents with more ELA.

Method

Participants

Participants were 80 adolescents (M_{age} = 13.86, SD_{age} = 1.84; 45.0% female) who were recruited from the community and over-sampled for ELA via targeted mass mailing to zip codes with high rates of poverty and community violence in Los Angeles and Orange Counties, California. Youth were not eligible to participate if they could not read or understand English, had a bleeding disorder (e.g., hemophilia), had any current or past major depressive episode, psychotic symptoms, mania, Autism Spectrum Disorder, any current chronic medical conditions (e.g., diabetes, cancer), or were regularly taking medications known to influence the immune system (e.g., inhaler, anti-histamines, anti-depressants).

Measures

Early life adversity.—Parents reported their child's exposure to ELA via semi-structured interview during the eligibility phone screen (Felitti et al., 1998). This 9-item checklist was adapted from the Adverse Childhood Experiences (ACE) questionnaire (Chapman et al., 2004; Dube et al., 2003), and included: financial insecurity affecting access to food or shelter, emotional abuse, witnessing domestic violence, parent separation/divorce, caregiver mental illness or substance use problems, family member in prison, death of a loved one, loss of home due to natural disaster, and serious personal injury. All *yes* responses were summed to create a total ACE score. Use of parent-reported ACE are consistent with the approaches used by the U.S. Department of Health and Human Services in the National Survey of Child and Adolescent Well-Being (e.g., Helton et al., 2022) as well as the National Survey of Children's Health (e.g., Crouch et al., 2019). Adolescents also self-reported ELA which showed moderate convergent validity with parent-reported ACEs (Kuhlman et al., 2022).

Inflammatory reactivity.—Inflammatory reactivity to the TSST-C was indexed by circulating IL-6 in plasma collected immediately before TSST-C initiation and 60 minutes thereafter. Circulating inflammatory responses to stress are reliably detected 35-120 minutes post-stress initiation, with changes in cytokines occurring 45-120 minutes after stress onset occurring largely as a result of stress-induced changes in the white blood cell population and biosynthesis of cytokines following stress-induced changes in gene expression (Steptoe et al., 2007). Importantly, inflammatory markers were measured at 60 minutes after stress-onset because the sympathetic response to stress is thought to have largely resolved by this timepoint (Hermans et al., 2014). Further, adults exposed to childhood maltreatment

exhibit exaggerated IL-6 concentrations 60, 75, and 90 minutes post-TSST onset (Carpenter et al., 2010). IL-6 is the most sensitive inflammatory marker to acute laboratory stress (Steptoe et al., 2007). Consistent with this, IL-6 was the only inflammatory marker that showed an acute response to the TSST-C in our data. Specifically, after accounting for age, gender, BMI, and race/ethnicity, IL-6 increased from pre- to post-stress, $p = .019$, C-reactive protein and TNF-a did not, ps > .25. See Kuhlman and colleagues (2022) for more details about the inflammatory response to stress in this sample. All plasma samples from a participant were assayed on the same plate, in duplicate, at the UCLA Cousins Center for Psychoneuroimmunology. IL-6 was assayed via a multiplex assay utilizing a V-PLEX Custom Human Cytokine Proinflammatory Panel on the MSD electrochemiluminesence platform and Discovery Workbench software (MSD, Rockville, MD). Samples were assayed at a 2-fold dilution according to the manufacturer's protocol, with an eight-point standard curve with tripling dilutions. The lower limit of detection (LLOD) was 0.20 pg/mL for IL-6; 0.8% of samples were below the LLOD and those observations were replaced with 50% the LLOD or 0.10 pg/mL. Inter-assay coefficients of variation (CVs) were less than 10% and intra-assay CVs were less than or equal to 5%.

Balloon Analog Risk Task (BART).—Participants completed the Balloon Analog Risk Task as a measure of risk tolerance in pursuit of rewards (Lejuez et al., 2002). There were 30 trials, during each of which the participant saw a red balloon on the screen. The participant was instructed to pump up the balloon as many times as they would like and that they would earn an additional 5 cents with each additional pump. However, they were also reminded that balloons pop if they are pumped up too much and that they would lose all of their earnings for any balloons that popped. The number of allowable pumps before the balloon popped varied across trials and was randomly determined. Figure 2 provides a visual overview of the BART. Each trial included a button they could push to collect their earnings and move on to the next balloon. In line with the recommendations of the task's authors (Lejuez et al., 2002), as well as the extant literature (See Lauriola et al., 2014 for meta-analysis), analyses focused on total adjusted pumps which is the total number of pumps the participant made across the task on balloons that did not pop, and average adjusted pumps per trial in which the balloon did not pop. The rationale for this is that behavioral responses on trials that did pop were artificially constrained by the explosion and the number of additional pumps the participant would have made is unknown and cannot be estimated. High values on either of these outcomes reflected high tolerance for the risk of loss in pursuit of rewards while low values on these outcomes reflected low tolerance for the risk of losing money earned in the current trial. This task reliably activates neurocircuitry involved in reward motivation including the insula, putamen, and prefrontal cortex, particularly among adolescents (Wang et al., 2022), and uses a similar behavioral measure of motivation for rewards as is used in preclinical experiments (i.e. number of lever presses; Berridge et al., 2009). Importantly, performance on this task is also sensitive to stressful contexts (Johnson et al., 2012).

Pirate Task.—Participants completed the Pirate Task to measure reward learning as measured by the development of a response bias in favor of high relative to low value trials (Galvan et al., 2005). In each of the 90 trials, participants saw one of 3 pirates, and

these 3 pirates were randomly assigned either a low (0.10 points), medium (0.5 points), or high value (1 point). Points accumulated throughout the task and each point was equivalent to an additional entry in a raffle for $50. In each trial, a single pirate appeared on either the left or the right side of the screen for 1000ms, followed by a 2000ms delay. After the delay, a treasure chest appeared on the screen prompting the participant to indicate whether the last pirate they saw was on the left or right side of the screen by pushing the *O* or *P* key on the keyboard. Failure to respond within 2000ms was recorded as an error and the task advanced to the next trial. Participants received feedback after each trial indicating that their response was "Correct!" or "Wrong", and for all correct trials their total points accumulated was shown on the screen. Figure 2 provides a visual overview of the Pirate Task. Reward response bias was operationalized as the difference in accuracy on high relative to low value trials and reaction times for accurate high relative to low value trials, with larger differences indicating that the participant was more sensitive to trials with higher reward values. Importantly, there were no differences in accuracy or reaction time when comparing high and low value trials during the first 20% of the task at either pre- or post-stress (pre-stress accuracy $p = 0.95$ and latency $p = 0.92$ and post-stress accuracy $p = 0.31$ and latency $p = 0.41$), suggesting that any overall response bias was learned over the course of the task. Accuracy and latency on high and low value trials across the pre- and post-stress administrations of the task are shown in Supplemental Figures 1 and 2, respectively.

Color-word Stroop Task.—Participants also completed the color-word Stroop task (Stroop, 1935). This task was included to determine the specificity of our findings to reward processes above and beyond basic cognitive functions, and because acute increases in inflammation have been associated with processing speed on this task (Brydon et al., 2008; Harrison et al., 2009). Participants completed 84 trials in which a color word (red, green, blue, or black) appeared on the screen written in either red, green, blue, or black font. The participant was required to indicate the color the word was written in while ignoring the meaning of the word. For example, if the word GREEN appeared on the screen in red font, the participant was to indicate that the word was red while inhibiting the meaning of the word. Processing speed was indexed by participant reaction time on congruent trials (e.g., the word GREEN appearing in green font) and inhibitory control was indexed by reaction times on incongruent (e.g., the word GREEN appeared in red font) relative to congruent trials.

Procedures

Participants were recruited via mass-mailing based on census records of households with children between 12-15 years living in the Los Angeles and Orange County area. Interested parents completed a phone interview to determine eligibility. In order to over-sample for ELA, mass mailing over-sampled from zip codes with poverty and violent crime rates that exceeded the national medians based on publicly available census and police report data. A total of 97 participants were enrolled in the study overall, however only 80 (83.5%) had IL-6 observations at both pre- and 60-minutes post-stress. Data from youth in the present analyses did not differ from that ofyouth excluded for missing IL-6 reactivity data with respect to sex, race, ethnicity, parent education, household income, familial home ownership, age, BMI, or ELA, all ps > 0.41.

Eligible participants completed a single laboratory visit beginning between 1-4 PM to control for circadian effects on immune and psychological function. All participants and their parents provided written, informed consent upon arrival to the laboratory. A nurse measured the participant's height and weight before inserting an in-dwelling catheter for blood collection. The Trier Social Stress Test for Children (TSST-C) was administered to induce psychosocial stress (Buske-Kirschbaum et al., 1997). The TSST-C involved having trained judges enter the participant's experimental room, instructing the participant that they would be given the beginning of a story and have 5 minutes to develop an "exciting ending" to that story which would be compared against all of the other participants in the study. The judges then left the experiment room for 5 minutes, then returned to hear the participant's story for 5 minutes. Throughout the 5-minute speech delivery judges were trained to not provide any supportive non-verbal or verbal feedback (i.e. smiling, laughing, nodding) and if the participant stopped speaking before 5 minutes had elapsed, the judges would prompt the participant by saying, "You still have time. Please continue." At the end of the 5 minutes, the judges then asked the participant to serially subtract 7 from 758 for 5 minutes. Each time a participant made an error in their calculation, the judges would say "Error. The correct answer was XXX. Please start again at 758."

Blood was collected immediately before, then 60 and 90 minutes after TSST-C initiation via an in-dwelling catheter. Between the end of the TSST-C and the 60-minute blood collection, participants watched a nature documentary to engage their attention but facilitate recovery. Reward tasks were administered 90 minutes before and 60 minutes after stress onset. See Figure 1 for an overview of laboratory procedures.

Data analysis.—All analyses were conducted in SPSS version 28. Hypotheses were tested using mixed linear models with trials nested within participants. First, we estimated total adjusted pumps, adjusted average pumps, and reward response bias measured in accuracy then reaction time in separate models as a function of time (pre- vs. post-stress), IL-6 at each timepoint, and their interaction (indexing change in IL-6). We then tested whether ELA moderated the association between change in IL-6 and each outcome. ELA was entered into the models as a continuous variable and figures depicting results plot ELA above and below the mean ELA score in the sample (ELA = 2). Exploratory analyses probed interactions where $p < .10$ and simple slopes were reported in order to facilitate comparisons with other studies. However, only results where $p < .05$ were considered statistically significant and interpreted. Simple slopes of change in IL-6 (time x IL-6) for participants below (ACE ≤ 1) and above (ACE ≥ 2) the median ELA in the sample (ACE = 2) were computed to facilitate interpretation of any interactions.

All models included random effects of time and within-person IL-6, and, all models accounted for the fixed effect of between-person IL-6, age in years, sex, BMI, and race/ethnicity—consistent with expert consensus recommendations for research involving inflammatory biology (O'Connor et al., 2009). Between-person IL-6 was computed as the average IL-6 concentration for each person across the protocol centered around the grand mean of IL-6. Further, ELA was related to some but not all of these covariates. Specifically, ELA exposure was higher among male participants, $p = .037$, and higher among Hispanic and black participants, $p = .006$. ELA was not related to age, $p = .44$, or BMI, $p = .90$.

Results

Participant characteristics are reported in Table 1. Table 2 provides descriptive statistics for each task before and after stress. Supplemental Table 1 and Supplemental Figures 3 through 9 summarize and show distributions of raw variables for within-person IL-6 and all behavioral outcomes. Participants showed significant increases in negative affect as well as decreases in positive affect from immediately before to immediately after the TSST-C, Δ negative affect = 2.31 (SD = 4.44) t = 5.04 p < .001 95% CI [1.46, 3.16] and Δ positive affect = −2.23 (SD = 5.39) t = −4.02 p < .001 95% CI [−3.31, −1.19]. Adolescents showed a reliable but modest inflammatory response to the stressor; 75% of participants showed an increase in IL-6 from 0 to 60 minutes. IL-6 concentrations were 0.60±0.44 pg/mL at baseline and 0.74±0.48 pg/mL at 60 minutes; change in IL-6 Cohen's $d = 0.33$ *95%CI*[0.02, 0.64] (See Kuhlman et al., 2022 for more details).

ELA was not associated with any of the behavioral outcomes at pre-stress: total adjusted pumps, $p = .35$, adjusted average pumps, $p = .75$, accuracy or reaction time to high relative to low value trials on the Pirate Task, $p = .21$ and $p = .57$ respectively, processing speed, $p = .20$, or inhibitory control, $p = .10$.

Risk tolerance in pursuit of rewards

Contrary to hypotheses, IL-6 reactivity was not associated with changes in behavioral responses on the BART, specifically the number of pumps on trials where the balloon didn't pop, adj. total pumps $b = -22.17$ (*SE*=142.69), $p = .88$ and adj. pumps per trial $b = 1.09$ (*SE*=9.34), $p = .91$ (Table 3).

Consistent with hypotheses, however, ELA moderated the association between IL-6 reactivity and change in behavior on the BART from pre- to post-stress, specifically for total pumps across the task, $b = -275.09$ (*SE*=79.15), *95%CI*[−440.70, −109.49], $p = .003$. Among adolescents in the sample exposed to higher ELA, IL-6 reactivity was associated with decreases in total pumps from pre- to post-stress, $b = -462.83$ (*SE*=231.56), *95%CI*[−926.69, 1.04], $p = .05$, relative to adolescents with little to no ELA, $b = 288.95$ (*SE*=215.93), *95%CI*[−147.09, 724.98], $p = .19$. See Figure 3 for adjusted total pumps by IL-6 reactivity separately for youth exposed to low and high ELA, and Figure 4 for a clustered boxplot of observed Total Pumps (adjusted) by time, IL-6 reactivity, and ELA.

A similar but nonsignificant trend was observed for average pumps per trial, such that ELA moderated the association between IL-6 reactivity and change in average pumps per trial from pre- to post-stress, $b = -10.73$ (*SE*=6.01), *95%CI*[−22.65, 1.18], $p = .077$. IL-6 reactivity was associated with a trend toward decreases in average pumps per trial from pre- to post-stress among adolescents exposed to high ELA, $b = -21.24$ (*SE*=12.05), *95%CI*[−45.53, 3.06], $p = .085$, but not among youth with low ELA, $b = 9.12$ (*SE*=14.23), *95%CI*[−19.87, 38.10], $p = .53$.

Reward response bias

Contrary to hypotheses, IL-6 reactivity was not associated with changes in accuracy on high relative to low value trials from pre- to post-stress in the Pirate task, $b = -0.001$ (*SE*=.015)

95%CI[−.03, .028], $p = .94$. However, greater IL-6 reactivity was associated with slower reaction times to correct trials with high relative to low value, $b = -53.76$ (*SE*=25.29) *95%CI*[−103.34, −4.19], $p = .034$.

Consistent with hypotheses, ELA moderated the association between IL-6 reactivity and accuracy on high relative to low value trials from pre- to post-stress, $b = 0.02$ (*SE*=.01) *95%CI*[.001, .04], $p = .042$. Among adolescents exposed to high ELA, greater IL-6 reactivity was associated with non-significant decreases in accuracy for high relative to low value trials, $b = .03$ (*SE*=.02) *95%CI*[−.02, .07], $p = .24$, whereas among adolescents exposed to low ELA greater IL-6 reactivity was associated with non-significant increases in accuracy for high relative to low value trials, $b = -.03$ (*SE*=.02) *95%CI*[−.07, .01], $p = .16$. Figure 5 shows the association between IL-6 reactivity and change in reward response bias from pre- to post-stress separately for youth exposed to low and high ELA. Figure 6 provides a clustered boxplot of observed accuracy for high relative to low value trials by time, IL-6 reactivity, and ELA.

ELA did not moderate the effect of IL-6 reactivity on reward response bias as measured by reaction time on correct high relative to low value trials, $b = 24.65$ (*SE*=18.25) *95%CI*[−11.13, 60.42], $p = .18$. See Table 4 for results of the adjusted models predicting accuracy and latency on the Pirate Task.

Processing speed and inhibitory control

IL-6 reactivity was not associated with changes in processing speed, $b = 122.61$ (*SE*=196.89) *95%CI*[−268.23, 513.46], $p = .54$, or inhibitory control, $b = -402.59$ (*SE*=201.58) *95%CI*[−1363.70, 558.53], $p = .20$. Nor was the effect of IL-6 reactivity on processing speed or inhibitory control moderated by ELA, $b = -52.29$ (*SE*=133.72) *95%CI*[−319.39, 214.82], $p = .70$, and $b = -386.35$ (*SE*=142.13) *95%CI*[−832.02, 59.33], $p = .07$, respectively.

Discussion

The purpose of this study was to examine the effects of stress-induced inflammation on risk tolerance in pursuit of rewards and bias for high relative to low value rewards in an adolescent sample, and to determine whether ELA moderated these associations. Largely consistent with the neuroimmune network hypothesis (Nusslock and Miller, 2015), ELA moderated neuroimmune communication for both risk tolerance in pursuit of rewards as measured on the BART and reward response bias on the Pirate Task. This was the first study to show altered neuroimmune communication among ELA-exposed adolescents in the context of acute psychosocial stress, and its implications for depression and its pathogenesis follow.

In contrast with existing studies on immune activation and reward motivation (Boyle et al., 2020, 2019; Draper et al., 2018), no main effect of inflammatory reactivity was observed for adjusted pumps on the BART in the present sample, representing the absence of an overall association between increases in inflammation and reward motivated behavior. However, the effect of inflammatory reactivity on adjusted pumps did vary by ELA such that greater IL-6

reactivity was associated with increases in pumps observed among youth exposed to low ELA but not among youth exposed to high ELA. Importantly, this was the most reliable observation from the study and survives a correction for multiple comparisons across all of the behavioral tasks administered and outcomes analyzed. Consistent with the neuroimmune network hypothesis (Nusslock and Miller, 2015), ELA may desensitize individuals to the impact of inflammatory signaling on willingness to expend effort for rewards relative to protecting existing resources. Reward motivation in the context of acute inflammatory reactivity is often conceptualized using the sickness behavior model, which posits that acute increases in inflammatory activity serve to reorient an individual to preserve resources by limiting reward pursuit to those that are necessary for survival (Dantzer and Kelley, 2007). Yet, empirical tests of this hypothesis in humans have been limited to adult populations (Boyle et al., 2020, 2019; Draper et al., 2018; Lasselin et al., 2016) and have generated mixed results, depending on the immune stimulus and task used. Importantly, the BART reflects reward motivation in the context of the risk of loss which may have contributed to the divergence of our findings from other studies using reward motivation tasks without any risk of loss (e.g., Treadway et al., 2009). However, it is important to note that reward tasks often include trials in which no reward is received which is what occurred on trials where the balloon popped, and our results were independent of the number of balloon pops a participant experienced. The implications of attenuated reward motivated behavior in the context of risk, stress, and inflammation during adolescence may be considerable. Adolescence is a sensitive period of social development in which academic, extracurricular, and occupational achievements shape opportunities in adulthood. For example, risk tolerance in pursuit of rewards may be essential to which adolescents have the psychological resources to pursue mastery in new skillsets and cultivate meaningful social relationships. Yet, youth exposed to ELA may be at a psychobiological disadvantage in the absence of inflammation-induced facilitation of reward pursuit, particularly in stressful contexts to which they are more frequently exposed.

This study also examined the role of stress-induced inflammatory activity on reward response bias. Youth in our sample with little to no ELA demonstrated an increase in reward response bias (faster performance on high relative to low value trials) in the context of stress-induced inflammation, whereas those with high ELA showed no change in response bias as a function of inflammatory reactivity. This observation is somewhat consistent with two studies showing that IL-6 reactivity following the influenza vaccine and psychosocial stress have been associated with an increase in response bias during implicit reward learning (Boyle et al., 2020, 2019). Notably, acute increases in IL-6 following endotoxin were not associated with changes in reward response bias (Draper et al., 2018) which may suggest that inflammation-induced changes in reward response bias are more readily observed in the context of mild changes in inflammatory signaling. The effect of IL-6 reactivity on reward response bias among the low ELA participants may converge with the sickness behavior model, such that inflammation facilitated more behavioral evidence of awareness of which trials were associated with larger rewards. In the context of sickness or acute inflammation, sensitivity to differences in reward value may be an essential cognitive and perceptual step to successfully modulating behavior in ways that optimize for easy to attain or highly valuable rewards. Youth with high ELA did not show this pattern and instead demonstrated

low reward response bias throughout the protocol, regardless of IL-6 reactivity. Again, this may indicate a psychobiological disadvantage among ELA-exposed youth in which their behavior is relatively insensitive to variability in reward value across contexts (i.e., stress, acute inflammation) that may be physically and cognitively costly.

There are several interdependent neurobiological processes that may explain why adolescents exposed to ELA show differential reward processing in the context of stress-induced inflammation. These include changes to dopaminergic and glutamatergic activity, altered microglia function, and aberrant development of the PFC. The effect of inflammatory signaling on reward is thought to occur, in part, through dopaminergic activity in the mesolimbic pathway (see Treadway et al., 2019 for review). Acute increases in inflammation decrease the availability of dopamine within this neural circuit as a result of inflammation-induced changes to metabolic functions throughout the body. The resident immune cells of the brain, microglia, are responsible for pruning dopamine receptors during adolescence (Kopec et al., 2018), a process that is central to social development. ELA has been shown in preclinical experiments to lead microglia to over-prune dopamine receptors (Catale et al., 2022). Indeed, a meta-analysis of studies linking ELA to dopaminergic markers in preclinical experiments found that ELA decreases dopamine precursors and increases dopamine metabolites specifically within the striatum (Bonapersona et al., 2018). Neuroinflammation can also have profound excitatory and even excitotoxic effects on neural function via glutamate (Béchade et al., 2013; Miller et al., 2013; Pascual et al., 2012). There is a long-standing hypothesis that stress-related psychiatric diseases are the result of altered glutamatergic signaling to and from the PFC (Haroon et al., 2014; Haroon and Miller, 2017; Moghaddam, 2002). Notably, one consequence of glutamatergic activity in the PFC is dopamine depletion in the nucleus accumbens and ventral striatum (Moghaddam, 2002). ELA has also been specifically linked to alterations to fronto-cortical brain regions, such as the PFC, which exhibit a prolonged period of maturation and are therefore more vulnerable to environmental influences (Pechtel and Pizzagalli, 2010). In response to the same situations and challenges, ELA-exposed individuals exhibit less connectivity between subcortical regions (i.e., amygdala or striatum) and the regulatory neural resources available in the PFC (Gee et al., 2013; Gianaros et al., 2011; Herringa et al., 2013; Sheridan et al., 2012). Together, these neurobiological processes may drive the multifarious sequelae of ELA, particularly in the context of stress. Indeed, ELA was not associated with any of our reward measures at pre-stress, and only emerged at post-stress in the context of stress-induced increases in IL-6.

The results of this study should be considered in the context of its limitations. First and foremost, this was a within-subjects design where all participants underwent a psychosocial stress task and all participants served as their own comparison. The causal role of stress cannot be inferred nor the specific role of inflammatory signaling. That being said, changes in inflammation as well as subjective ratings of positive and negative affect following the TSST-C in this study were similar to those observed in studies comparing these outcomes against a placebo or other control condition (Allen et al., 2014; Steptoe et al., 2007). Yet, negative affective and IL-6 responses to the TSST-C were not correlated, change in NA – change in IL-6 $r = -0.14$, $p = .32$, suggesting that participants who reported the largest increases in negative affect were not necessarily the participants who showed the largest

increases in IL-6. This is consistent with what has been observed in the broader stress reactivity literature (Campbell and Ehlert, 2012), and suggests that our results reflect a physiological process that is not driven simply by the subjective negative affective response to psychosocial stress. Furthermore, some of the changes in performance from pre- to post-stress were likely the result of practice effects for the tasks themselves rather than changes in the psychological processes the tasks were designed to measure. Inflammatory activity is known to interfere with learning (Yirmiya and Goshen, 2011), thus it is possible that inflammatory responses also contributed to individual differences in any practice effects observed across the protocol, though we did not see evidence to this effect on processing speed or inhibitory control. The TSST-C is a mild psychosocial stressor that is likely comparable in severity to common daily stressors that adolescents face in academic and social settings. For this reason, the observed changes in each psychological domain were small and therefore only fairly robust effects of inflammatory reactivity on each of these outcomes would have been detectable. It is also important to note that risk tolerance in pursuit of rewards as measured on the BART is confounded by the threat of loss (i.e., task involves explicit warnings that balloons pop if pumped too much). This differs from reward motivation tasks that dominate the literature and were developed for adult populations (Draper et al., 2018; Treadway et al., 2009). Finally, this study focused on the role of inflammatory signaling in psychological responses to stress. ELA has been shown to moderate the effect of other peripheral stress markers on cognitive and affective processes (e.g., cortisol; Kuhlman et al., 2021b, 2021a), as well as to moderate the effects of inflammation following stimulation with the influenza vaccine (Kuhlman et al., 2020b), suggesting that the moderating role of ELA may not be specific to inflammatory processes or stress.

Conclusions

This is the first study to our knowledge to demonstrate that ELA moderates the association between stress-induced inflammation and reward processes in an adolescent sample, notably without a history of depression. ELA has been associated with increased risk for depression and suicide in adulthood (Chapman et al., 2004; Green et al., 2010; Kessler et al., 2010c). Understanding the psychobiological pathways of risk and onset during adolescence, when risk for MDD is rapidly rising (Kessler et al., 2010a, 2010b; Kessler and Bromet, 2013), are critical to the identification of modifiable pathways that can be leveraged for prevention. In particular, ELA has been linked to widespread dysregulation in reward-related psychological and neural processes which may provide insight into the types of interventions that may mitigate risk among ELA-exposed youth. Indeed novel interventions, such as Positive Affect Therapy (Craske et al., 2019, 2016; Meuret et al., 2022), which leverage the effectiveness of cognitive-behavioral therapy as well as the advances in our transdiagnostic understanding of reward dysregulation, may be ideal for preventing stress-related psychopathology among ELA-exposed youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- First study to examine stress-induced inflammation in distinct reward sub-domains in a pediatric sample
- Stress-induced inflammation decreases risk tolerance in pursuit of rewards among ELA-exposed adolescents
- Stress-induced inflammation increases bias toward high relative to low-value rewards among adolescents with low ELA

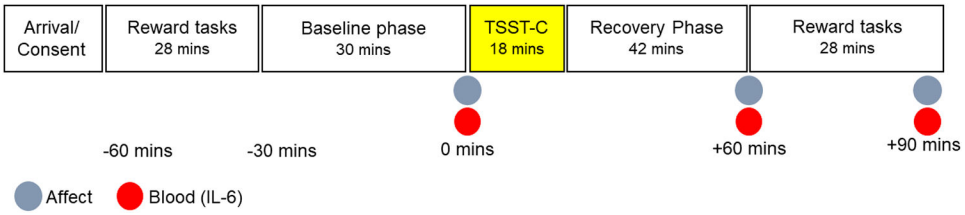

Figure 1.
Laboratory visit procedures

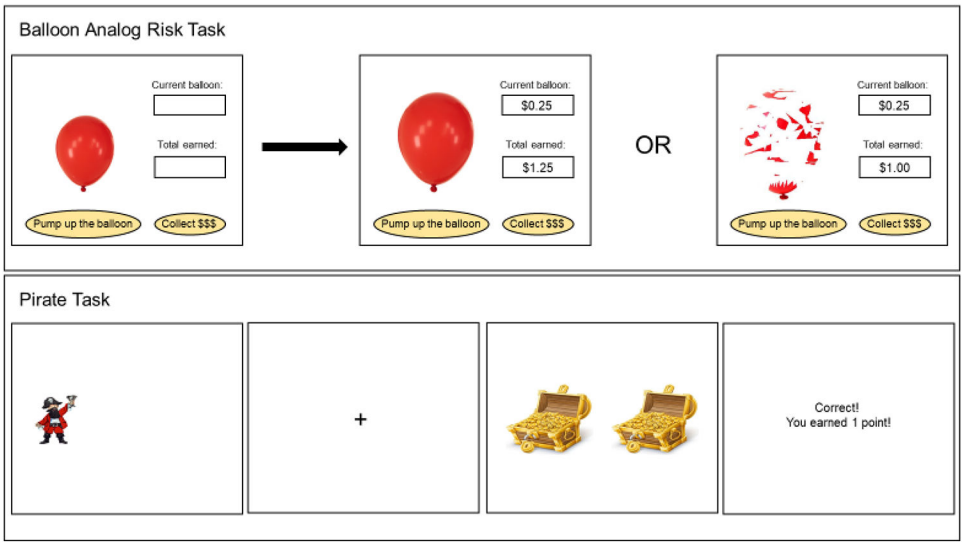

Figure 2.
Overview of Balloon Analog Risk and Pirate Tasks.

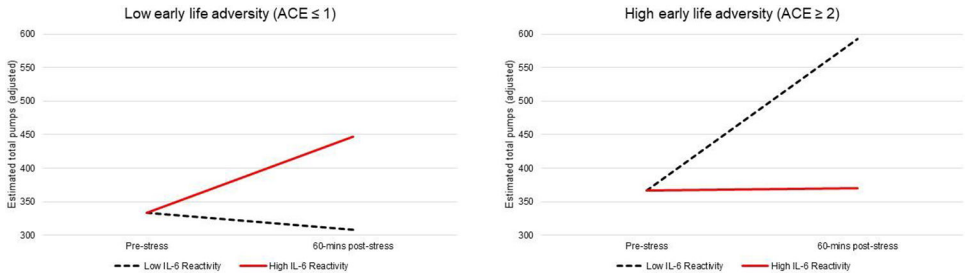

Figure 3.

Estimated pre- to post-stress change in risk tolerance by inflammatory reactivity and by ELA.

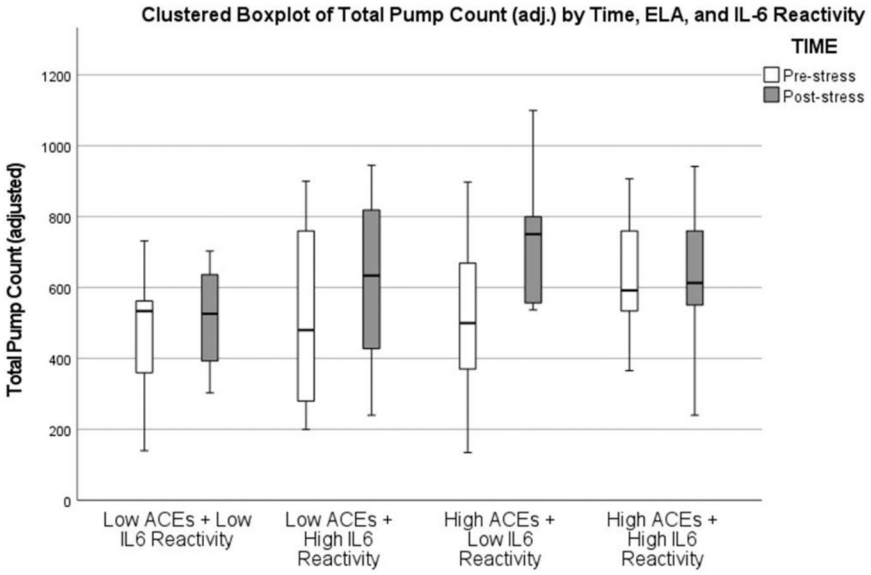

Figure 4.
Observed total pumps (adjusted) by time, IL-6 reactivity, and ELA

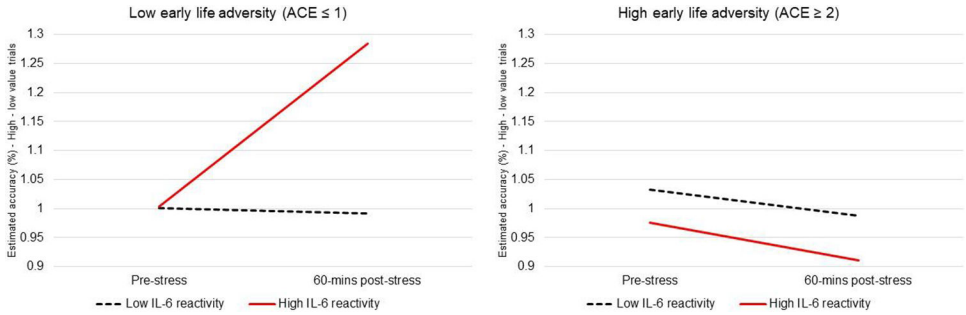

Figure 5.

Estimated pre- to – post-stress change in reward response bias by inflammatory reactivity and ELA.

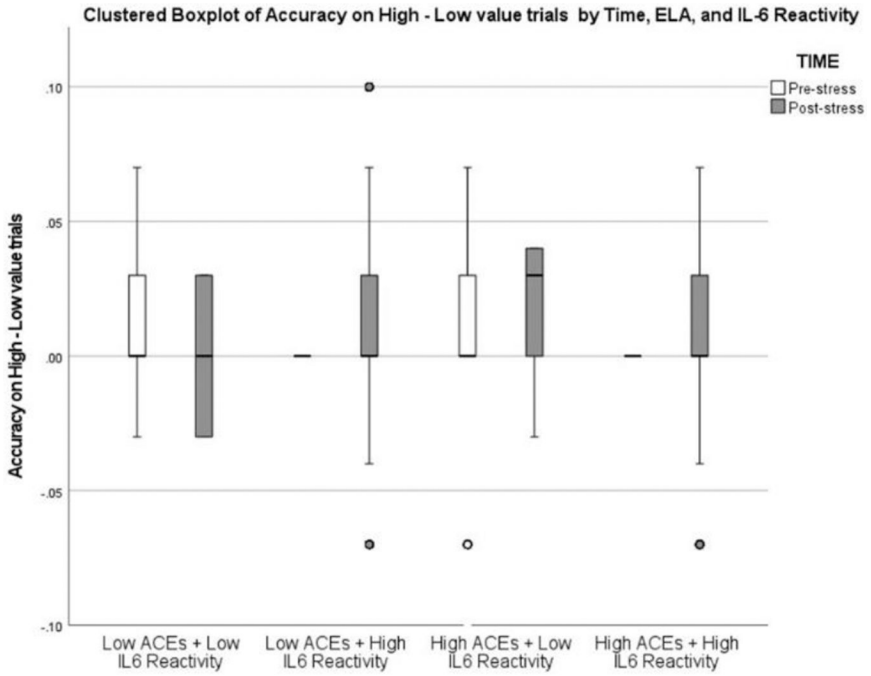

Figure 6.
Observed accuracy on high-low value trials by time, IL-6 reactivity, and ELA

Table 1.

Participant characteristic (n=80)

	M (SD)	% (n)
Age	13.86 (1.54)	
Body mass index (BMI)	21.46 (4.25)	
Pubertal Development Score (PDS)	8.23 (2.20)	
Female		45.0 (36)
Race/Ethnicity *		
Asian		8.8 (7)
Black		8.8 (7)
Hispanic/Latino		35.0 (28)
White		77.5 (62)
College educated mother		78.8 (63)
College educated father		75.0 (60)
Family household income		
<$50,000		12.5 (10)
$50,000-$100,000		20.0 (16)
>$100,00		65.0 (52)
Family owns home		67.5 (54)
Early life adversity (ELA)	2.01 (1.35)	
ELA = 0		11.3 (9)
ELA = 1		33.8 (27)
ELA = 2		18.8 (15)
ELA = 3		15.0 (12)
ELA = 4+		21.3 (17)

Note:

* Groups are not mutually exclusive.

Table 2.

Changes in affective processes pre- and 60-minutes post stress

	Pre-stress	60 mins post-stress	*p*-value
Inflammatory reactivity			
IL-6 (pg/ml), M(SD)	0.60 (0.44)	0.74 (0.48)	<.001
Risk tolerance			
Adj. Total pumps, M(SD) (ms)	576.61 (208.85)	655.00 (178.31)	.075
Adj. Average pumps, M(SD) (ms)	26.51 (13.27)	31.65 (11.61)	.10
Total balloons popped, M (SD)	7.08 (3.96)	8.34 (4.81)	.11
Reward Sensitivity			
Accuracy, %	99.1 (0.10)	97.6 (0.15)	.04
Latency, M(SD) (ms) (high - low value trials)	3.63 (12.25)	−2.12 (6.76)	.55
Processing speed *, M(SD) (ms)	−1179.54 (321.18)	−934.33 (208.63)	<.001
Inhibitory control, M(SD) (ms)	−335.01 (339.25)	−229.88 (204.45)	.035

Note:

*Values for processing speed were multiplied by −1 such that higher values = better processing speed or faster reaction times

Table 3.

Risk tolerance as a function of stress, inflammatory reactivity, and ELA

	Adjusted Total Pumps			Adjusted Pumps per Trial		
	b (SE)	***p***	***95%CI***	***b (SE)***	***p***	***95%CI***
Intercept	280.01 (236.00)	.24	−190.92, 750.95	−1.97 (16.57)	.91	−34.82, 30.88
Time (pre vs. post-stress)	45.07 (53.17)	.40	−61.47, 151.61	5.83 (2.61)	.027	0.66, 11.00
Within-person IL-6	36.29 (138.82)	.80	−243.86, 316.44	1.31 (5.50)	.81	−9.60, 12.21
ELA	20.69 (24.24)	.40	−27.74, 69.12	0.11 (1.44)	.94	−2.74, 2.97
Time x within-person IL-6	−545.55 (201.32)	.01	125.68, 965.41	17.92 (14.90)	.23	−11.60, 47.45
Time x ELA	18.55 (22.06)	.40	−25.60, 62.70	−.03 (1.11)	.98	−2.23. 2.17
ELA x within-person IL-6	28.90 (57.77)	.62	−87.35, 145.14	2.07 (2.55)	.42	−2.98, 7.12
Time x ELA x within-person IL-6	−275.09 (79.15)	.003	−440.70, −109.49	−10.73 (6.01)	.077	−22.65, 1.18

Note: Coefficient estimates reflect associations after accounting for age, sex, BMI, race/ethnicity, between-person variability in IL6.

Table 4.

Reward response bias as a function of stress, ELA, and inflammatory reactivity

	Accuracy (%)			Latency (ms)		
	b (SE)	***p***	***95%CI***	***b (SE)***	***p***	***95%CI***
Intercept	1.00 (0.04)	<.001	−.92, 1.08	216.66 (183.07)	.24	−149.97, 583.30
Time (pre- vs. post-stress)	−0.03 (0.02)	.24	−0.08, 0.02	13.69 (30.07)	.65	−46.91, 74.28
Value (Low, medium, high)	0.01 (0.005)	.16	−0.003, 0.02	9.40 (8.36)	.26	−6.98, 25.79
ELA	−0.0003 (0.05)	.95	−.01, 0.01	−16.50 (16.92)	.34	−51.16, 18.15
Within-person IL-6	.01 (.02)	.58	−.03, .06	−109.93 (70.51)	.13	−255.79, 35.93
Value x ELA	−0.003 (.002)	.17	−.01, .001	−2.11 (3.55)	.55	−9.07, 4.86
Value x within-person IL-6	.003 (.01)	.79	−.02, .03	38.85 (21.43)	.07	−3.16, 80.85
ELA x within-person IL-6	−.001 (.01)	.90	−.02, .02	39.67 (31.65)	.22	−24.72, 104.07
Time x value	−.005 (.01)	.47	−.02, .01	−17.20 (10.95)	.12	−38.67, 4.26
Time x ELA	.002 (.01)	.85	−0.02, .02	−17.82 (12.51)	.16	−43.05, 7.41
Time x within-person IL-6	.001 (.13)	.99	−.25, .25	208.68 (167.72)	.22	−134.83, 552.19
Value x within-person IL-6 x ELA	−.005 (.01)	.44	−.02, .01	−12.21 (9.88)	.22	−31.58, 7.16
Time x ELA x value	.004 (.003)	.18	−.002, .01	6.09 (4.51)	.18	−2.76, 14.93
Time x ELA x within-person IL-6	.01 (.05)	.84	−.09, .11	−47.03 (66.19)	.48	−183.16, 89.11
Time x value x within-person IL-6	−.04 (.03)	.10	−.09, .01	−91.39 (44.12)	.04	−177.88, −4.91
Time x value x ELA x within-person IL-6	.02 (.01)	.04	.001, .043	24.65 (18.25)	.18	−11.13, 60.42

Note: Coefficient estimates reflect associations after accounting for age, sex, BMI, race/ethnicity, and the between-person effect of IL-6