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Reward Sensitivity, Cognitive Response Style, and Inflammatory Response to an Acute Stressor in Adolescents

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Authors' Contributions

DPM generated hypotheses, ran and interpreted analyses, and drafted the manuscript; TN participated in data analysis, result interpretation, and provided feedback on the manuscript; EC participated in data analysis, result interpretation, and provided feedback on the manuscript; BAM participated in the creation of the database, data cleaning, and provided feedback on the manuscript; LME participated in the design, cleaning of the inflammation data, and provided feedback on the manuscript; CLC assayed blood samples, aided in database construction, and provided feedback on the manuscript; LYA helped write the grant that funded the study, and provided feedback on the manuscript; LBA helped design the original study and write the grant that funded the study, participated in the design and coordination of this study, and helped to write and provided feedback on all drafts of the manuscript. All authors read and approved the final manuscript.

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Data Sharing Declaration

The datasets generated and/or analyzed during the current study are not publicly available but may be available from the corresponding author on reasonable request.

Conflicts of Interest

The authors report no conflict of interests.

Ethical approval

The Temple University Institutional Review Board approved the protocol (IRB protocol #6844).

Informed Consent

Written informed consent was collected from all study participants after explaining their role in the study and before starting data collection.

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Abstract

Inflammation is gaining support as a biological mediator between stress and many negative outcomes that have heightened risk during adolescence (e.g., mood disorders). Thus, an important line of inquiry is evaluating whether risk factors for mood psychopathology also are associated with heightened inflammatory responses to stress during this developmental period. Two prominent risk factors that interact to predict mood psychopathology are reward sensitivity and perseverative cognitive response styles, which also have been associated with heightened inflammatory proteins. These factors could influence inflammation by synergistically amplifying stress reactivity. Ninety-four late adolescents (Mage = 18.3 years, range = 15.6 – 21.9 years) completed measures of reward sensitivity, cognitive response style, and blood draws before and 90-minutes after a modified Trier Social Stress Task to determine levels of inflammation. Higher reward drive interacted with more perseverative response style ratios (rumination relative to distraction + problem-solving) to predict larger increases in interleukin-6 (a proinflammatory protein). Follow-up analyses found that reward drive interacted with all three components of the ratio to predict change in interleukin-6. Thus, these results suggest that high reward drive and perseverative cognitive response styles are associated with increased inflammatory response to social stress in adolescents, a potential physiological mechanism linking these risk factors to mood psychopathology during this developmental period.

Introduction

Psychological stress confers risk for multiple negative health outcomes. Stress is associated with a heightened risk and worse course of many medical illnesses, including respiratory infections, cardiovascular disease, and autoimmune diseases such as HIV/AIDS (Cohen et al., 1991, 2007). Additionally, stress is implicated in the pathophysiology of many psychopathologies such as mood, anxiety, substance use, and externalizing disorders, many of which develop in middle to late adolescence (Costello et al., 2012; Kessler et al., 1997). Inflammation, an important component of the biological stress response that prepares the body to heal injuries and illness, may be a mechanism mediating the relationship between stress and illness (Slavich & Irwin, 2014).

Many proteins are involved in the inflammatory response, including acute phase proteins (e.g., C-reactive protein (CRP)) and proinflammatory cytokines (e.g., interleukin (IL)-6, interleukin-8, and tumor necrosis factor alpha (TNF α)), as well as anti-inflammatory cytokines (e.g., interleukin-10), which regulate inflammation. Chronically high levels of inflammation can be maladaptive (Barton, 2008). For example, elevated inflammation has been associated with many negative outcomes that increase in prevalence during adolescence (e.g., depression; Moriarity et al., 2019; Moriarity, Kautz, et al., in press a).

Much of the research on psychosocial predictors of the inflammatory stress response has used adult samples. Given the importance of adolescence in the developmental trajectory of many psychological and biological health outcomes, this gap is important to fill. Specifically, this study will test part of an immunocognitive model (first described in Moriarity, et al., 2018), in which the tendency to perseverate on distress amplifies the association between arousal-related risk factors (in this study, reward drive [described below]) and inflammation in ways that increase risk for mood psychopathology. Investigating malleable characteristics such as perseverative cognitive styles and reward-oriented behavior/cognitions during adolescence can identify potential targets for intervention and increase understanding of the pathophysiology of stress-related disorders (e.g., depression and bipolar disorder, both of which are associated with perseverative cognitions and abnormal reward drive) during this important developmental period. In addition to the potential for treatment, testing this model during adolescence, a period of elevated risk for a plethora of negative outcomes, also could have preventative implications for recurrent conditions that otherwise would continue into adulthood. Finally, previous work supporting this model (specifically, the finding that rumination moderates the association between reward sensitivity and inflammation [Moriarity, Ng, et al., in press b]) was carried out in emerging adults. Thus, extending this model to an adolescent sample, which is the aim of the current study, is important to evaluate the developmental specificity of this theory.

Individual differences in inflammatory stress reactivity

Repeated and prolonged activation of inflammatory processes, via physical or psychological stress, can increase risk for the chronically elevated inflammation associated with negative outcomes (Miller et al., 2002). Consequently, investigation of psychological predictors of inflammatory stress reactivity may provide insight into the development of chronically elevated inflammation and associated illnesses. Several studies utilizing laboratory-based social stressors involving social conflict, rejection, and exclusion have found increases in inflammatory biomarkers post-stressor (Kemeny, 2009). However, little work has been done investigating characteristics that might impact inflammatory stress reactivity, particularly in adolescents. Although there is much work to be done in this area, this review will focus on rumination and reward sensitivity because of the risk they confer for mood disorders, for which adolescence is a critical period of risk (Alloy et al., 2006; Kessler et al., 2012).

Reward Sensitivity is Associated with Inflammation

Both high and low reward sensitivity (conceptualized as the strength of reward processing and approach motivation) have been associated with elevated inflammation (see Nusslock & Miller, 2016 for a review). One potential way that elevated reward sensitivity could influence inflammatory profiles is by increasing the salience of goal-pursuit or failures (see Alloy & Nusslock, 2019, which also described potential mechanisms linking inflammation and reward sensitivity that are beyond the scope of this paper). In particular, reward drive, the facet of reward sensitivity that involves the intensity with which one pursues goals and desired outcomes, might be associated with inflammatory stress reactivity to reward/goal-associated stressors. Supporting this theory, heightened reward sensitivity is associated with increased negative affect when goal-striving is frustrated (Hundt et al., 2013). Considered

with findings that negative affect predicts larger stress-evoked changes in inflammatory biomarkers such as interleukin-6 (Carroll et al., 2011), it is plausible that reward sensitivity may amplify inflammatory stress responses to reward-salient events, such as performance-based social interactions. In support of this, competitive social interactions (e.g., performances perceived to be competing against other peers, such as the Trier Social Stress Task (TSST)) are associated with increases in proinflammatory cytokine activity in young adults (Chiang et al., 2012).

Cognitive Response Style is Associated with Inflammation

The perseverative cognition hypothesis (Brosschot et al., 2006) postulates that repeated focusing on stressors can amplify physiological reactions to psychological distress, prolonging stress-related activation and contributing to a shift in physiological regulation. This view is supported by research finding that adults instructed to ruminate (the response to distress that involves repetitively focusing on the distress and on possible causes/consequences of a distressing situation) after a laboratory stressor had larger increases in C-reactive protein, and a slower recovery to baseline, compared to participants instructed to engage in distraction (Zoccola et al., 2014). Although this study supports that different cognitive responses to stress modulate inflammatory stress reactivity, it fails to consider the potential interplay between various cognitive response styles during stressful situations. Theoretically, individuals can fluctuate between engaging in perseverative (e.g., rumination) and non-perseverative (e.g., problem-solving, distraction) cognitive responses to negative affect as they attempt to regulate their emotions. Analytic methods that account for the degree to which individuals engage in perseverative vs. non-perseverative cognitive response styles might more accurately reflect naturally occurring cognitive processes.

One technique to address this is to analyze ratios of perseverative (e.g., rumination) to non-perseverative cognitive responses (e.g., problem-solving + distraction), which have been demonstrated to better predict some outcomes than single response styles alone (e.g., depression; Abela, Aydin, & Auerbach, 2007). This approach has the potential to capture the tendency for an individual to use multiple response styles in response to negative affect (e.g., intermittently attempting to distract or problem-solve to avoid rumination). However, it is important to note that ratio variables introduce some difficulty in interpretation (e.g., an individual high in both rumination and non-perseverative response styles could have the same ratio as an individual low in both rumination and non-perseverative response styles). Although this technique captures the degree to which an individual engages in perseverative vs. non-perseverative cognitions, comparing results using ratio scores to supplemental analyses using scores for the individual response styles can help clarify interpretation.

The Interaction Between Reward Sensitivity and Cognitive Response Style

The above review describes how reward drive and rumination may influence inflammation in ways that could confer risk for negative medical and psychological outcomes. However, little work has evaluated reward sensitivity or rumination alone, or in combination, as predictors of acute inflammatory responses in adolescents. The immunocognitive model (Moriarity, et al., 2018) posits that perseverative response styles amplify the effect of arousal-related characteristics on inflammation in ways that increase risk for negative

outcomes (specifically mood psychopathology). Given that individuals with high reward drive tend to experience heightened arousal during goal pursuit and perceive reward or performance-related stressors to be more salient (Alloy & Nusslock, 2019), it is plausible that perseverating on negative affect during goal-oriented stress amplifies the association between reward drive and inflammatory stress responses.

Moriarity, Ng, and colleagues (in press b) found initial support for the interaction between reward sensitivity and ruminative response style as a predictor of resting levels of inflammatory proteins in young adults (specifically, C-reactive protein and interleukin-8). Importantly, this study also found that reward sensitivity and ruminative response style interacted to predict both hypo/manic and depressive symptoms. However, this study did not account for potential cognitive strategies that reduce perseveration, such as problem solving or distraction, which might buffer this effect. Further, this study did not test whether reward sensitivity and cognitive response style would interact to predict acute inflammatory stress responses, one potential mechanism through which these variables might influence basal levels of inflammatory proteins. Thus, it is important to investigate the interaction of these psychological risk factors in the context of an acute laboratory stressor. Further, as mid and late adolescence are important windows of risk for an array of psychopathologies (Costello et al., 2012), extending this work to an adolescent sample is critical for testing the developmental sensitivity of this theory.

Hypotheses

This study sought to integrate two established risk factors for mood psychopathology, reward sensitivity and perseverative cognitive response styles, into a model of inflammatory stress reactivity (indexed by change in C-reactive protein, interleukin-6, interleukin-8, interleukin-10, and tumor necrosis factor alpha following a stressor). Because the current study utilized a performance-based social stress task that included no receipt of reward, our hypotheses are specific to reward drive. It was hypothesized that reward drive would interact with the ratio of perseverative cognitive response styles to negative affect (rumination on negative affect/[problem-solving + distraction from negative affect]) to predict increases in inflammatory proteins from pre- to post-stress task. Specifically, higher reward drive would predict larger increases in inflammatory proteins post-stress in individuals with more perseverative response styles. Significant models using the ratio variable were followed up with identical models testing the individual cognitive response styles. It was hypothesized that high reward drive would interact with higher rumination, but lower problem solving and distraction, to predict greater increases in inflammatory proteins post-stress task.

Method

Participants and Procedures

Participants were drawn from the Adolescent Cognition and Emotion (ACE) project, a longitudinal study of the development of depressive disorders in adolescence. Following Temple University Institutional Review Board approval (protocol No. 6844) as well as permission from the Philadelphia School District to contact potential participants, 12- to 13-year-old adolescents ($N = 640$) and their mothers/primary caregivers were recruited from the

greater Philadelphia area through a combination of mailings to families with children attending middle schools (68% of the total sample) and advertisement in local newspapers (32% of the sample). Inclusion criteria were: (a) the adolescent was aged 12–13; (b) the adolescent self-identified as Caucasian/White, African American/Black, or Biracial (one of the primary aims of Project ACE was to investigate differences in depression etiology between these three racial groups); and (c) the mother/primary caretaker was willing to participate in the study. Participants were excluded if either child or mother/primary caretaker had (a) insufficient skill in the English language to complete the assessments or (b) a severe psychiatric, developmental, or learning disorder (Alloy et al., 2012). Written informed consent or assent (for the adolescents) was obtained from all participants.

The present sample included a subset of adolescent participants ($n = 99$) who had measures of trait reward sensitivity and cognitive response styles, blood collection prior to and after a modified Trier Social Stress Task (mTSST, an optional component of the ACE study added several years after starting data collection), and complete demographic and health information. Ten participants were removed due to signs of acute inflammatory activity at the baseline blood draw on the day of the mTSST, as indexed by a C-reactive protein value > 10 mg/L (Bell et al., 2017; de Ferranti et al., 2006), resulting in an N of 89 for the analytic dataset. Additionally, all analyses were rerun excluding an additional ten participants who reported medical diseases known to affect the immune system or inflammatory physiology (e.g., allergies, asthma, sickle cell anemia), as a sensitivity analysis to evaluate whether inclusion of these conditions influenced results. The pattern of primary and follow-up results (in terms of significance and direction) was the same in both samples, so in an effort to report the most well-powered analyses, only the results with C-reactive protein baseline values > 10 mg/L removed are described below.

Measures of trait reward sensitivity and cognitive response styles were selected from the visit closest to the date of the mTSST ($M = 8.5$ months, $SD = 9.6$ months). Internal consistencies for the measures were calculated using the data in this analytic subsample, but the 8.5 month retest reliabilities were calculated using the total ACE sample, as the timepoints used in this study only have one timepoint of measurement for reward sensitivity and cognitive response style. Mean age at the time of the mTSST was 18.3 years ($SD = 1.4$ years, range = 15.6 – 21.9 years) and the final sample was 50.6% female, 37.1% Caucasian, and 62.9% African American. Pearson's chi-square tests indicated that the analytic subsample did not differ at baseline from the total ACE sample on gender ($\chi^2 = .240$, $p = .624$), but the analytic sample had a higher proportion of African Americans than the total sample ($\chi^2 = 4.637$, $p = .031$). An independent samples t-test found that the analytic sample did not differ from the total ACE sample on family income; $t(609) = -.1567$, $p = .118$.

Measures

Reward sensitivity.—The Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scales (Carver & White, 1994) were used to measure individual differences in trait sensitivity to rewards. Participants responded to 20 questions on a 4-point Likert scale ranging from *strongly disagree* to *strongly agree*. The scales consist of a BIS subscale and three BAS subscales: Reward Responsiveness, Drive, and Fun-Seeking. Because the acute

stress task used in this study involves social performance to be compared against peers, without any receipt of reward, the Drive subscale (example item: “When I want something, I usually go all-out to get it”) was the only subscale used in analyses as it is most directly related to arousal during goal-pursuit/performance situations ($\alpha = .77$ in this sample, 8.5 month retest reliability = .57 in the total ACE sample).

Response styles.—The Children’s Response Styles Questionnaire (CRSQ; Abela, Vanderbilt, & Rochon, 2004) is a self-report instrument that measures how youth respond to sad/depressive moods. It consists of 25-items (e.g., “When I am sad, I think about how sad I feel”) measuring the frequency with which dysphoria is responded to with rumination, distraction, or problem-solving. Items were rated on a 4-point Likert scale (“Almost never”, “Sometimes”, “Often”, and “Almost always”). The CRSQ has demonstrated good validity and internal consistency (Abela et al., 2004). The scale consists of 3 subscales: rumination ($\alpha = .93$ in this sample, 8.5 month retest reliability = .69 in the total ACE sample), distraction ($\alpha = .70$ in this sample, 8.5 month retest reliability = .50 in the total ACE sample), and problem-solving ($\alpha = .80$ in this sample, 8.5 month retest reliability = .55 in the total ACE sample). As recommended by previous research (Abela et al. 2007), this study utilized the CRSQ ratio scores to operationalize response styles, with higher ratio scores reflecting a greater tendency to engage in rumination relative to distraction and problem-solving. CRSQ ratio scores were calculated by dividing the rumination subscale by the sum of the problem-solving and distraction subscales. Follow-up analyses used the three component scores in isolation.

Social Stress Test.—The TSST is a widely used and valid method to induce psychosocial and physiological stress responses (Hankin et al., 2010; Kirschbaum et al., 1993). It includes public speaking and mental arithmetic tasks. This study used a slightly modified adolescent version of the TSST (mTSST) protocol developed by Hankin et al. (2010) to better suit our adolescent sample. Participants were instructed to give a 3-minute speech about why they should be accepted into a social group of their choice (e.g., a basketball team) in front of a camera (where they saw themselves on a screen) and a confederate. They also were told that their speech would be video recorded, and their performance rated by an expert panel of judges, with an award for good speeches. Prior to beginning the speech, participants were instructed to think about and prepare their speech for five minutes while the interviewer left the room. After giving the three-minute speech, participants then completed a calculation task (subtracting increments of 13 from a starting value of 2,083) for 60-seconds. Blood was drawn before and 90-minutes after the mTSST. This duration was chosen because it is associated with peak interleukin-6 (a protein frequently used in depression research, the central aim of Project ACE) reactivity in response to the TSST (Carpenter et al., 2010; Pace et al., 2006).

Inflammatory proteins.—Blood samples were collected by certified phlebotomists using antecubital venipuncture into 10 mL vacutainers designed for freezing plasma separated from the cells within the vial (BD Hemogard with K2 EDTA). Vacutainers were stored in an ultracold freezer at -80°C and thawed on the day of assay.

Four cytokines were quantified by multi-cytokine array (interleukin-6 (IL-6), IL-8, IL-10, and tumor necrosis factor alpha (TNF α)), and high-sensitivity C-reactive protein (CRP) was determined in singleplex assay, using an electrochemiluminescence platform and a QuickPlex SQ 120 imager for analyte detection (Meso Scale Discovery, Gaithersburg, MD). These biomarkers were selected because of their common usage in depression research, the primary aim of Project ACE. Each specimen was assayed in duplicate, with intra-assay coefficients of variation between 1.94 – 4.38%, and values referenced to a standard curve generated from 7 calibrators with known concentrations. The lower limit of detection (LLOD) for the cytokines was 0.1 pg/mL, with a large dynamic range up to 2000 pg/mL. CRP is present in blood at higher concentrations, and thus, plasma was diluted to correspond to the standard curve. Values were converted to mg/L units in keeping with the clinical literature, and were calculated down to 0.1 mg/L (Breen et al., 2011; Dabitao et al., 2011).

Data Analysis Plan

All descriptive statistics, correlations, and analyses were conducted in SPSS (v23; IBM Corp, 2016). All moderation analyses were conducted using Model 1 in the Process Macro (Hayes, 2013). Bivariate correlations between demographic and physical characteristics and primary study variables were calculated. Paired samples t-tests were conducted to determine which inflammatory biomarkers significantly increased in response to the mTSST.

One *a priori* hypothesis was tested. A moderation analysis examined whether BAS drive interacted with more perseverative cognitive response style ratios to predict increases in inflammatory biomarkers from pre- to post-mTSST. Analyses controlled for baseline levels of the protein in the model (to account for change) and months between measurement of the predictor variables and the mTSST, as well as variables that have been associated with stress reactivity: gender and income (Raffington et al., 2018) and race and age (Hostinar et al., 2014). However, it is important to note that, because of the lack of work investigating demographic differences in inflammatory responses to the TSST, these citations are for investigations of demographic characteristics with cortisol stress reactivity (which is associated with inflammatory stress reactivity). Only inflammatory biomarkers that increased significantly in response to the mTSST were used as outcome variables in this analysis. Significant results were probed to identify whether specific cognitive response styles were driving the associations and to aid in the interpretation of the results with the cognitive ratio variable. Additionally, significant results were probed using the Johnson-Neyman technique (Hayes, 2013), which identifies regions of significance of the moderator (cognitive response style) for the conditional main effect of the predictor (BAS drive) on the dependent variable (change in inflammatory proteins).

Results

Preliminary Analyses

Descriptive statistics and bivariate correlations for the primary study variables are in Table 1. IL-6 and IL-8 showed significant increases from pre- to post-mTSST ($t(88) = 5.150, p < .001$, 95% CI = .0867 – .1956; $t(88) = 2.499, p = .014$, 95% CI = .1979 – 1.7340, respectively), but CRP, IL-10, and TNF α did not (p 's = .472, .934, .670, respectively).

Primary Analyses

Consistent with our hypothesis, high BAS drive interacted with more perseverative cognitive response style ratios to predict larger increases in IL-6 to the mTSST ($b = .085$, $SE = .027$, $t = 3.165$, $p = .002$, 95% CI = .0314 – .1381; see Fig 1). The Johnson-Neyman technique probing this effect identified a region of significance above the 81st percentile of the cognitive response style ratio ($b = .029$, $SE = .015$, $t = 1.991$, $p = .050$, 95% CI = .0000 – .0586), with more perseverative relative to non-perseverative cognitive styles amplifying the association between high BAS drive and increases in IL-6. There was also a region of significance below the 10th percentile of the cognitive response style ratio ($b = -.036$, $SE = .018$, $t = -1.991$, $p = .050$, 95% CI = -.0725 – .0000), such that less perseverative relative to non-perseverative cognitive styles buffered the association between high BAS drive and increases in IL-6. However, the interaction between drive and cognitive response style ratio did not significantly predict changes in IL-8 post-mTSST ($p = .943$). The interaction predicting IL-6 was robust to Holm-Bonferroni corrections (Holm, 1979, adjusted $p = .004$).

Follow-up Analyses

The three components of the cognitive response style ratio were tested independently, in interaction with BAS drive, as predictors of change in IL-6. All three follow-up analyses were significant and in the directions predicted. The interaction between BAS drive and rumination predicted change in IL-6 ($b = .003$, $SE = .001$, $t = 2.048$, $p = .044$, 95% CI = .0001 – .0052), such that drive predicted greater increases in IL-6 as rumination increased. The Johnson-Neyman technique identified a region of significance above the 95th percentile of rumination ($b = .055$, $SE = .027$, $t = 1.991$, $p = .050$, 95% CI = .0000 – .1092), with more rumination amplifying the association between high drive and increases in IL-6. The interaction between BAS drive and problem-solving significantly predicted change in IL-6 ($b = -.007$, $SE = .003$, $t = -2.130$, $p = .036$, 95% CI = -.0136 – -.0005), such that drive interacted with lower levels of problem-solving to predict greater increases in IL-6. The Johnson-Neyman technique identified a region of significance in the bottom 3rd percentile of problem-solving ($b = .047$, $SE = .023$, $t = 1.991$, $p = .050$, 95% CI = .0000 – .0931), such that at lower levels of problem-solving, high drive predicted greater increases in IL-6. Likewise, the interaction between BAS drive and distraction significantly predicted change in IL-6 ($b = -.010$, $SE = .004$, $t = -2.718$, $p = .008$, 95% CI = -.0172 – -.0027), such that high drive interacted with lower levels of distraction to predict greater increases in IL-6. The Johnson-Neyman technique identified regions of significance below the 20th percentile ($b = .033$, $SE = .017$, $t = 1.991$, $p = .050$, 95% CI = .0000 – .0656), such that at lower levels of distraction, high drive predicted greater increases in IL-6. There was also a significance region above the 87th percentile of distraction ($b = -.048$, $SE = .024$, $t = -1.991$, $p = .050$, 95% CI = -.0966 – .0000), such that high levels of distraction buffered the association between high drive and increases in IL-6.

Discussion

This study supports the value of considering both reward sensitivity and perseverative response style in predicting inflammatory responses to acute, performance-related stressors in adolescents. Consistent with the *a priori* hypothesis, as the ratio of ruminative compared

to problem solving + distraction responses to negative affect increased, higher reward drive predicted larger interleukin-6 responses to the modified Trier Social Stress Task. Follow-up analyses found that high levels of rumination and low levels of non-perseverative response styles (problem solving and distraction, separately) amplified the association between higher drive and increases in interleukin-6. Additionally, higher levels of non-perseverative relative to perseverative cognitive response styles and higher levels of distraction buffered the positive association between reward drive and increases in interleukin-6. Thus, this study provides consistent evidence that perseverative cognitive styles amplify, and non-perseverative cognitive styles buffer, the risk that high reward drive confers for elevated inflammatory responses to social stress.

These results extend previous findings showing that these psychological variables interact to be associated with circulating baseline inflammatory proteins in adults (Moriarity, Ng, et al., in press b, which did not include a stress task) to also predict acute inflammatory stress responses in adolescents. This demonstrates that the elevated inflammation associated with reward hypersensitivity might be due in part to inflammatory stress reactivity, rather than being purely accounted for by reward-related lifestyles (e.g., substance use; Alloy et al., 2009). Additionally, Moriarity and colleagues' (in press b) support for a reward x rumination interaction was in a sample of young adults. Given the developmental changes that occur in the key constructs of these studies (e.g., neural regions associated with reward; Gabard-Durnam et al., 2014), it is important to test this theory in samples of different ages to investigate the developmental robustness of the associations. This is particularly true for adolescence, a period of risk for many inflammation-related negative outcomes (e.g., mood disorders). Taken together with the support of this model in an adult sample (Moriarity, Ng, et al., in press b), the current study supports the immunocognitive model (with respect to reward processing) as a potentially valid model of risk for elevated inflammation from adolescence into young adulthood.

Additionally, results provide further evidence for considering perseverative cognitions and arousal-related characteristics as risk factors for heightened inflammation, and potentially, for associated psychopathology (e.g. depression, Moriarity et al., 2018). Further, these results highlight cognitive response styles as a potential intervention target (both in terms of reducing rumination and increasing problem solving and distraction) to buffer against the inflammatory effects of stressful situations, particularly in individuals with elevated reward drive. Similarly, reducing reward drive or increasing insight into when and how to modulate the pursuit of goals might be a useful intervention target as well. Identifying treatment, and ideally prevention, targets in adolescents is particularly critical as early-onset of depression and bipolar disorder (among many other inflammation-related outcomes) are frequently associated with more negative outcomes (Hammen et al., 2008; Post et al., 2014).

It is of interest that this immunocognitive model was predictive for interleukin-6, but not for interleukin-8. This may be due to study methods, as a blood draw 90-minutes post-modified Trier Social Stress Task was chosen because of the established interleukin-6 reactivity for this duration (Carpenter et al., 2010; Pace et al., 2006) and because interleukin-6 is commonly used in depression research, which was the primary aim of Project ACE. In addition, there are a number of important differences in cytokine tissue sources and

biological actions. Interleukin-6 is known to be a pleiotropic cytokine, produced by many different tissues, including lymphoid cells as well as fat and liver cells, with diverse actions throughout the body. Thus, it is commonly used in biobehavioral research because of its responsiveness. In contrast, interleukin-8 found in blood is likely to derive from other cellular sources, including skin cells and the monocyte/macrophage lineage, and although it has many biological actions, the stimulation of neutrophils is its most commonly described function (Dixit & Simon, 2012; Hedges et al., 2000). Further, these biomarkers have different interactions with the HPA-axis, with interleukin-6 frequently demonstrating a stronger relationship to this component of the biological stress response (Turnbull & Rivier, 1999). Although it is possible that distinct linkages between each cytokine and the psychological processes under study exist, it seems more parsimonious to account for the better prediction of interleukin-6 on the basis of its tissue sources and physiological actions and the time lag that was chosen for the study.

This study had several important strengths. First, it assessed a diverse community sample of adolescents, a group in a critical developmental period that is under researched in psychoneuroimmunology. Second, participants exhibited levels of reward sensitivity that varied across the entire dimension. Third, this study took multiple cognitive response styles and their interplay into consideration by using a ratio to more accurately reflect the numerous response styles that can be employed in a stressful situation. Fourth, as social feedback is of increased salience to adolescents (Bronfenbrenner, 1986) and the modified Trier Social Stress Task involves a speech to earn a place in a desired social group and evaluation of social performance, this is an ideal sample and stressor with which to test the impact of reward drive on inflammatory stress reactivity.

However, these results should be considered in light of the following limitations. First, there was some variation in timing of self-report measures and the modified Trier Social Stress Task ($M = 8.5$ months, $SD = 9.6$ months). Although the questionnaires are believed to assess trait reward sensitivity and cognitive response styles, it is not known if the associations between these variables and inflammatory proteins vary across different time lags (e.g., as with depression; Moriarity et al., 2019). Also, in the total ACE sample, 8.5 month retest reliability was modest for some of the subscales used in this study. Further, an important future direction would be to replicate these results with measures that assess cognitive response styles specifically in response to the acute stressor. Additionally, the use of a ratio variable introduces difficulty in separating which processes might be driving observed effects (e.g., high rumination with high problem solving + distraction would have a similar ratio as low levels of these three components). However, this concern is ameliorated by follow-up tests investigating the individual effects of the component cognitive response styles, which were all significant and in the directions hypothesized. A future study with more power should test the three-way interaction between rumination, cognitive response styles that reduce perseveration, and reward drive in predicting inflammatory stress reactivity. Also, the current study design precluded the investigation of potential effects of inflammatory stress reactivity on reward sensitivity. Furthermore, responses to the modified Trier Social Stress Task and other stressful challenges can be influenced by life events that were not taken into consideration, such as the experience of childhood adversity (Harkness, Stewart, & Wynne-Edwards, 2011). Finally, although interleukin-6 frequently is considered

proinflammatory, it has a large range of functions and can even act in an anti-inflammatory manner. Although this isn't a limitation of this study's methods, it is important to consider when interpreting results.

Conclusion

Inflammation is steadily gaining traction as a transdiagnostic risk factor for many negative outcomes associated with adolescence (e.g., mood disorders). However, little work has examined malleable characteristics that modulate inflammatory stress reactivity that might serve as intervention targets in treating and preventing disorders secondary to elevated inflammation. This study extends previous work showing that reward sensitivity and cognitive response styles synergistically predict basal levels of inflammatory proteins (Moriarity, Ng, et al., in press b) by demonstrating their joint utility in predicting the interleukin-6 response to an acute performance-based social stressor in a sample of late adolescents. Results suggest that relatively perseverative cognitive response styles and a heightened sensitivity to reward may interact to contribute to the emergence of subclinical inflammatory propensities. This may help to explain the commonly reported associations between reward sensitivity, cognitive vulnerabilities, and inflammation in a variety of psychiatric disorders that emerge in adolescence (e.g., depression and bipolar spectrum disorders) and highlights cognitive response styles and reward drive as potential intervention targets. Developmentally, extending previous work in young adults to find synergistic combinations of reward sensitivity and perseverative response styles predicting inflammatory processes in an adolescent sample provides initial evidence that this interaction may be relevant across these periods of development. Future work should test this theory in a dataset that allows a statistical approach with more developmental implications to examine whether these associations are time invariant from adolescence through young adulthood.

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Fig 1.

BAS Drive and CRSQ ratio (Rumination/(Problem-Solving + Distraction)) interact to predict change in IL-6 post-Trier Social Stress Task

Note: Predictors are centered, CRSQ = Children's Response Style Questionnaire, IL = interleukin, pg/L = picogram/Liter, Low = -1 SD from mean, Moderate = mean, High = +1 SD from mean.

Table 1.**Bivariate Correlations and Descriptive Statistics of Primary Study Variables**

Measure	1.	2.	3.	4.	5.	6.	7.
1. CRSQ Ratio	—						
2. Drive	-.06	—					
3. IL-6 Baseline (pg/mL)	.09	-.05	—				
4. IL-6 Diff (pg/mL)	-.04	.02	.07	—			
5. IL-8 Baseline (pg/mL)	.02	.19	.14	.10	—		
6. IL-8 Diff (pg/mL)	-.03	.04	-.03	-.09	-.24*	—	
7. Age (years)	.04	.09	-.09	.11	.27**	-.02	—
N	89	89	89	89	89	89	89
Mean	.98	10.71	.39	.14	3.29	.97	18.30
SD	.40	2.17	.39	.26	1.59		1.35
Range	.33–2.13	5.00–16.00	.08–2.26	-.71–1.26	.82–8.41	-2.21–33.08	15.62–21.89

Note: CRSQ Ratio= Children's response style ratio, IL- = Interleukin, BMI = Body Mass Index, Diff = Difference between baseline and post-mTSST

**
 $p < .01$