Effects of stress-induced inflammation on reward processing in healthy young women

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ABSTRACT

Background: Anhedonia, or loss of interest or pleasure, is a feature of depression and transdiagnostic construct in psychopathology. Theory and compelling evidence from preclinical models implicates stress-induced inflammation as a psychobiological pathway to anhedonic behavior; however, this pathway has not been tested in human models. Further, although anhedonia may reflect dysregulation in multiple dimensions of reward, the extent to which stress-induced inflammation alters these dimensions is unclear. Thus, the current experimental study used a standardized laboratory stressor task to elicit an inflammatory response and evaluate effects of stress-induced inflammation on multiple behavioral indices of reward processing.

Methods: Healthy young women (age 18–25) completed behavioral reward tasks assessing reward learning, motivation, and sensitivity and were randomized to undergo an acute psychosocial stressor (n = 37) or a no-stress active control (n = 17). Tasks were re-administered 90–120 min post-stress to coincide with the peak of the stress-induced inflammatory response. Blood samples were collected for assessment of the pro-inflammatory cytokine interleukin-6 (IL-6) at baseline and 90 and 120 min post stressor.

Results: Stress-induced IL-6 was associated with increased response bias during reward learning and increased motivation when probability of receiving a reward was low. Sensitivity to reward in the context of a motivation task was not altered in association with stress-induced IL-6.

Conclusions: Contrary to hypotheses, mild increases in IL-6 following acute stress were associated with increased reward responsiveness during reward learning and selective increases in motivation. Results contribute to an emerging and nuanced literature linking inflammatory response to reward processing, and demonstrate that behavioral effects of stress-induced inflammation may be detected in the laboratory setting.

Clinical trial registration: NCT03828604.

1. Introduction

Anhedonia, or diminished interest or pleasure, is a transdiagnostic feature of psychopathology (Romer Thomsen et al., 2015; Foti and Baskin-Sommers, 2015; Kashdan, 2004; Bedwell et al., 2014) and core diagnostic symptom of Major Depressive Disorder (American Psychiatric Association, 2013). Anhedonia is of particular interest in depression because it may precede and increase vulnerability for depression (Loes, 1996; Pizzagalli, 2014; Gotlib et al., 2010; Rawal et al., 2012) and predicts poor treatment response (Vrieze et al., 2013; Craske et al., 2016). Anhedonia is increasingly recognized as a multidimensional construct, reflecting deficits in reward motivation, learning, and/or sensitivity (Romer Thomsen et al., 2015), each of which may warrant different pharmacological and behavioral therapeutic approaches (Craske et al., 2016; Nutt et al., 2006). However, the psychobiological mechanisms that give rise to dysregulation in the reward system have yet to be elucidated.

Stress is a well-established and robust predictor of depression onset and recurrence (Kendler et al., 2003; Monroe and Reid, 2009; Hammen, 2015) and is linked specifically with alterations in reward-related processes (Cavanagh et al., 2010; Perelli et al., 2012; Treadway et al., 2013; Harrison et al., 2016; Harrison et al., 2015; Eisenberger et al., 2010; Capuron et al., 2012; Draper et al., 2018; Lasselin et al., 2016;}

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Boyle et al., 2018). Stress also leads to increases in inflammation, which may be a critical pathway linking stress and reward dysregulation. Indeed, anhedonic behavior in animal models is reliably elicited by both chronic stress and inflammatory stimuli (Anisman et al., 2002; Yirmiya et al., 2015), and inflammation has been shown to mediate effects of chronic stress on sucrose preference in preclinical studies (Koo and Duman, 2008). Consistent with animal research, chronic stress and acute laboratory stressors are associated with reduced neural and behavioral reward responsiveness in humans (Bogdan and Pizzagalli, 2006; Berghorst et al., 2013; Bogdan et al., 2007; Kogler et al., 2015; Cavanagh et al., 2010; Porcelli et al., 2012; Treadway et al., 2013), and peripherally induced inflammation decreases neural response to novel stimuli and anticipation or receipt of monetary reward (Harrison et al., 2016; Harrison et al., 2015; Eisenberger et al., 2010; Capuron et al., 2012). However, inflammation has shown mixed associations with reward in humans when assessment is behavioral. For example, participants who receive endotoxin have been shown to exhibit decreased (Draper et al., 2018) and increased (Lasselin et al., 2016) reward motivation, with no effects on reward sensitivity. Similarly, while one study found enhanced performance on a reward learning task in association with increases in inflammation following vaccination (Boyle et al., 2018), null effects have also been reported (Harrison et al., 2016). Thus, it is not yet clear if certain reward dimensions are more sensitive to fluctuations in inflammation, or the conditions under which such effects are facilitative or inhibitory.

Furthermore, experimental assessment of inflammation and reward in humans has only been studied in the context of an induced peripheral inflammatory response, typically through administration of endotoxin or the typhoid vaccine. Endotoxin elicits an acute and robust peripheral inflammatory response that far exceeds the normative physiological changes that occur in response to repeated or chronic stress (Eisenberger et al., 2010; Draper et al., 2018; Lasselin et al., 2016; Dooley et al., 2018). The inflammatory response to typhoid vaccination is far milder and more inflammatory response (Johnson et al., 2005; Sugama et al., 2009), and anhedonic behavior is linked to increases in both peripheral (Ménard et al., 2017; Hodes et al., 2014) and central cytokines (Koo and Duman, 2008; Goshen et al., 2007) in preclinical models. A recent study in healthy women found that stress-induced increases in IL-6 were associated with changes in neural measures of reward responsiveness in a separate session (Treadway et al., 2017), but no previous studies have directly assessed effects of stress-induced inflammation on reward processing. However, this is feasible in the laboratory setting because acute laboratory stressors reliably elicit mild and delayed (90–120 min post stress) increases in the pro-inflammatory cytokine interleukin-6 (IL-6) (Marsland et al., 2017).

Thus, the goal of this study was to model a psychobiological pathway that is believed to be critical in understanding how stress may precipitate the transition to psychopathology by experimentally evaluating effects of stress-induced inflammation on behavioral measures of reward. To do so, we used a standardized acute psychosocial laboratory stressor, the Trier Social Stress Task (TSST) to elicit an inflammatory response and administered two well-established behavioral reward tasks, the Probabilistic Reward Task (PRT) (Tripp and Abop, 1999; Pizzagalli et al., 2005) and the Effort Expenditure for Rewards Task (EERT) (Treadway et al., 2009) at the peak of this inflammatory response (90–120 min post-stress). Given the preponderance of evidence from preclinical models and neuroimaging studies, and mixed evidenced from behavioral studies, we hypothesized that stress-induced inflammation would lead to decreases in reward processing across three dimensions of reward in both tasks (i.e., learning, motivation, and sensitivity).

2. Methods and Materials

2.1. Participants and procedure

Fifty-four healthy young women at the University of California-Los Angeles (UCLA) were recruited May–December 2017 through flyers
sensitivity to inflammatory challenge (Moieni et al., 2015). Exclusion
criteria included current illness, major medical conditions, current/past
alcohol use disorder, pregnancy, and use of tobacco or immune-antigen
medications. As shown in Fig. 1, 115 participants were assessed, 69
were eligible and randomized, and 54 provided valid blood samples and
behavioral data. Of these, 51 completed the EEVRT (n = 34 stress) and
44 provided evaluable PRT data (n = 31 stress).

After providing informed consent, participants completed ques-
tionnaires and the EEVRT during a baseline laboratory visit (Visit 1) and
were randomized 3:1 to the stress and control group via a computerized
random number generator. Within approximately two weeks (for 85% of
participants; range = 1–27 days), participants returned for Visit 2, which
lasted 3.5–4 h and was scheduled in the afternoon (starting 1:00–3:00 pm)
to control for diurnal variation in IL-6. Participants were instructed to re-
frain from exercising, eating, or drinking anything except water the hour
prior to Visit 2. They received reminder emails and a text the day of the
session and provided verbal confirmation of compliance. Upon arrival,
a nurse inserted an intravenous catheter in the antecubital vein of the par-
ticipant’s non-dominant arm. Participants first completed questionnaires
and reported on recent health behaviors that could potentially influence
levels of inflammation or the inflammatory response to stress (e.g., sleep,
alcohol and caffeine use, time since last meal). Participants then completed
the PRT and provided the first blood sample prior to undergoing the TSST
(Kirschbaum et al., 1993) or a placebo control task (Placebo (P)-TSST) (Het
et al., 2009). The TSST reliably activates the psychological and physi-
ological stress response (Frisch et al., 2015) and involves a challenging 5-min
speech and 5-min arithmetic task in front of two evaluators trained to
remain impassive and provide negative non-verbal feedback (Eisenberger
et al., 2010). The P-TSST has no evaluators and involves a 5-min speaking
task on a neutral topic and a 5-min counting task (Het et al., 2009). After
the TSST/P-TSST, participants watched a neutral movie until the PRT and
EEVRT were re-administered at 90–120 min post-TSST/P-TSST. Blood
samples were collected before, 90 and 120 min after the TSST/P-TSST.
Participants were compensated with course credit or $50, and task per-
formance was incentivized with money that participants received 4 months
after Visit 2. All study procedures were approved by the UCLA Institu-
tional Review Board (IRB); clinical trial registration NCT03828604.

2.2. Measures

2.2.1. Inflammation

Circulating concentrations of the pro-inflammatory cytokine IL-6 were
used to measure inflammation because IL-6 increases following the
TSST (Marsland et al., 2017), is elevated in individuals with de-
pression (Haapakoski et al., 2015), and is associated with changes in
reward processing and/or mood following an inflammatory stimulus
(Lassen et al., 2016; Boyle et al., 2018; Kuhlman et al., 2018). Blood
samples were collected by venipuncture into ethylenediamine tetra-
acetic acid tubes, placed on ice, centrifuged for acquisition of plasma
and stored at −80 °C. At study completion, samples were assayed for IL-
6 using a high sensitivity enzyme-linked immunosorbent assay (R&D
Systems, Minneapolis, Minn.). Samples were assayed in duplicate. Inter-
and intra-assay coefficients of variation were < 6%. The lower limit of
detection was 0.20 pg/mL, and there were no undetectable values.

2.2.2. Probabilistic reward task (PRT)

The PRT is a 15-min computerized task derived from signal detec-
tion theory which uses an asymmetric (3:1) pseudo-randomized rein-
forcement schedule to induce an implicit response bias towards one of
two ambiguous stimuli (see Supplementary Materials for additional
description of the PRT) (Tripp and Alsop, 1999; Pizzagalli et al., 2005).
Because the development of this response bias relies both on reward
sensitivity (i.e., immediate behavioral impact from reward feedback)
(Huys et al., 2013), the total PRT response bias score indexes an overall
reward responsiveness (e.g., Bogdan and Pizzagalli, 2006; Pechtel et
al., 2015). In the current study the PRT was administered before and 90-
min post-TSST/P-TSST onset during Visit 2.

2.2.3. Effort expenditure for rewards task (EEVRT)

The EEVRT (Treadway et al., 2009) is a computerized task that assesses
reward motivation and sensitivity to monetary reward. As previously
described (Treadway et al., 2009; Treadway et al., 2012a,b), the EEVRT
requires participants to choose between low and high effort trials. Low
effort trials require 30 button presses using the dominant index finger in 7 s
and are worth $1.00. High effort trials require 100 button presses with the pinky
finger of the non-dominant hand in 21 s and the reward varies from $1.24
–$4.30. Participants are told the task lasts for the same amount of time re-
gardless of the choices made, and that they will receive money for two
successfully completed trials that are randomly selected and summed (range
is $2.00 - $8.60). Participants are also told that only some trials will be
rewarded, and each trial presents the probability (12%, 50%, 88%) that
successful completion will be rewarded. If a choice is not made within 5 sec
the trial is randomly assigned.

Lower motivation for reward on the EEVRT is operationalized as less
willingness to exert greater effort for higher monetary reward and lower
sensitivity to reward is operationalized as an attenuated association be-
tween the extent to which variations in potential monetary reward
predict choice of high effort trials (Lassen et al., 2016; Treadway et
al., 2012). The EEVRT was shortened from 20 to 15 min in the current study
and was administered at Visit 1 and 120 min post TSST/P-TSST onset
during Visit 2. Of note, participants did not learn how much they had
earned for either EEVRT administration until the 4-month follow-up.

2.2.4. Psychosocial measures

Affect and fatigue were assessed using items from the Positive and
Negative Affect Schedule (Thompson, 2007; Watson and Clark, 1994)
and the fatigue subscale from the Profile of Mood States (McNair and
Lorr, 1971) pre- and post-TSST/P-TSST and with each blood draw
during Visit 2. Depressive symptoms and perceived stress over the past
week were assessed at the beginning of Visit 2 using the 20-item Center
for Epidemiologic Studies-Depression scale (Radloff, 1977) and the 10-
item Perceived Stress Scale (Cohen et al., 1983). Additional information
on psychosocial measures is available in Supplementary Materials.

2.3. Analytic approach

Analyses were conducted using Stata version 13.1. IL-6 values were
skewed and log transformed. Independent samples t-tests were used to
test for baseline differences between the TSST and P-TSST groups.
Multiple regression was used to verify group differences in affect fol-
lowing the TSST/P-TSST.

2.3.1. Mediation

Mediation analysis was used to evaluate effects of stress-induced
inflammation on behavioral measures of reward processing. The pre-
dictor of interest was group assignment (0 – P-TSST, 1 – TSST), the
mediator was change in IL-6 (IL-6 at 120 min minus IL-6 at baseline),
and the outcome was reward task performance (post-TSST/P-TSST
performance minus baseline performance). This analytic approach was
selected because it allowed us to model the experimental manipulation
and parsimoniously examine multiple components of the psychobiolo-
logical pathway. Specifically, the mediation analysis yielded coefficients
representing the extent to which group assignment predicted change in
IL-6, the extent to which changes in IL-6 predicted changes in reward
sensitivity.
using a non-parametric bootstrap approach \((n = 10,000\) samples) implemented using the \textsc{Stata} \texttt{paramed} module. This resampling method generates a coefficient for the mediated effect and bias-corrected bootstrap confidence intervals; the mediated effect is deemed significant if the confidence intervals do not include zero.

2.3.2. Task analyses: PRT

Consistent with prior work and current recommendations (e.g., Vrieze et al., 2013; Bogdan and Pizzagalli, 2006; Boyle et al., 2018; Pizzagalli et al., 2005; Pechtel et al., 2015), PRT data was cleaned using the following established inclusion criteria for evaluable data: accuracy greater than 50%; ratio of rewards received greater than 2.4; at least 80% trials within valid range (150 ms-2500 ms); < 16 outliers (after log transformation, trials with reaction times falling outside the mean +/− 3 standard deviations were considered outliers). Ten participants were excluded (18.5% of the sample) leaving a total of 44 participants \((n = 31\) stress).

**Assessment of change in reward responsiveness with the PRT.**

Reward responsiveness was operationalized as the total response bias score calculated across the 200 trials at each administration of the task (see Supplementary Material for formulas). Change in response bias was calculated by subtracting the total response bias score at pre-TSST/P-TSST from the total response bias score at post-TSST/P-TSST. This change score was the outcome variable for mediation analysis.

2.3.3. Task analyses: EEfRT

EEfRT trials that a participant did not complete within the 5-sec time limit were excluded (0.22% of all trials). Three participants did not complete the EEfRT due to time constraints. On average, participants successfully completed 96% of all trials that were chosen. Six participants completed < 79% of trials but were retained in analyses because incomplete trials were not due to low effort, as indicated by at least 80 out of 100 button presses on incomplete hard trials.

**Assessment of change in reward motivation with the EEfRT.** The proportion of high-effort trials chosen was calculated for the baseline assessment and the post-TSST assessment, consistent with past work (Lasselin et al., 2016; Treadway et al., 2009). A change score was calculated by subtracting the proportions chosen at Visit 1 from proportions chosen post-TSST/P-TSST at Visit 2; this change score was the outcome variable for the mediation model. Also consistent with prior studies, we calculated change scores at each of three levels of probability (low, medium, and high).

**Assessment of change in reward sensitivity with the EEfRT.** To evaluate effects of stress-induced inflammation on reward sensitivity on the EEfRT, generalized estimating equations (GEEs) with a binary logistic model and exchangeable working correlation structure were conducted within the stress group on EEfRT data collected at 120 min post-TSST. GEEs account for correlated data, are appropriate for a binary dependent variable (i.e., likelihood of choosing high-effort trials), and are a standard approach for analyzing EEfRT performance on a trial by trial basis (Treadway et al., 2009). The predictor of interest was a 2-way interaction term between reward magnitude and change in IL-6; this term allowed us to assess whether increases in reward magnitude predicted increased choice of high effort trials less robustly in the context of greater increases in IL-6.

2.3.4. Sample size calculation

Specifying an \(\alpha\) value of 0.05, a sample size of 57 was required to provide 80% power to detect a significant indirect effect in the mediation model. Sample size estimates come from Monte Carlo power analysis (Schoemann et al., 2017). Given the absence of previous work on stress-induced inflammation and behavioral measures of reward, estimates for standard deviations and correlations among the predictor, mediator and outcome variable were derived from pilot data in our lab (unpublished) as well as our prior work on peripheral IL-6 following vaccination and PRT performance (Boyle et al., 2018). We assumed a moderate correlation \((r = 0.5)\) between our predictor (TSST vs. P-TSST) and mediator (change in IL-6).

3. Results

3.1. Participant characteristics

Participants were on average 20 years old and of Latina, Asian, or Non-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sample Demographic and Psychosocial Characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ((n = 54))</td>
<td>Stress ((n = 37))</td>
</tr>
<tr>
<td>Ethnicity, N (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12 (22.2)</td>
</tr>
<tr>
<td>East Asian</td>
<td>13 (24.1)</td>
</tr>
<tr>
<td>Latina</td>
<td>18 (33.3)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Menstrual phase, N (%)</td>
<td></td>
</tr>
<tr>
<td>Menses</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Follicular</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Luteal</td>
<td>25 (47)</td>
</tr>
<tr>
<td>Use of hormonal contraception, N(%)</td>
<td>15 (28)</td>
</tr>
<tr>
<td>Academic Status, N (%)</td>
<td></td>
</tr>
<tr>
<td>Freshman</td>
<td>8 (14.8)</td>
</tr>
<tr>
<td>Sophomore</td>
<td>16 (29.6)</td>
</tr>
<tr>
<td>Junior</td>
<td>8 (14.8)</td>
</tr>
<tr>
<td>Senior</td>
<td>18 (33.4)</td>
</tr>
<tr>
<td>Post-graduate</td>
<td>4(7.4)</td>
</tr>
<tr>
<td>Parental Education, N (%)</td>
<td></td>
</tr>
<tr>
<td>Less than college</td>
<td>20 (37)</td>
</tr>
<tr>
<td>College or more</td>
<td>34 (63)</td>
</tr>
<tr>
<td>BMI, M (range)</td>
<td>23.05 (17.5-30.4)</td>
</tr>
<tr>
<td>Depressive symptoms, M (range)</td>
<td>13.41 (0-38)</td>
</tr>
<tr>
<td>Perceived stress, M (range) (\text{a})</td>
<td>18.39 (4-36)</td>
</tr>
</tbody>
</table>

*Note: M = mean; BMI = body mass index. Menstrual phase is missing for two participants and was assessed by asking participants to indicate the first
Table 2
Stress and Control Group Differences in Negative Affect, Positive Affect, and Fatigue After the TSST/P-TSST.

<table>
<thead>
<tr>
<th>Outcome (post-TSST/P-TSST)</th>
<th>Predictor</th>
<th>β</th>
<th>SE</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Affect</td>
<td>Group</td>
<td>3.66</td>
<td>0.26</td>
<td>1.71</td>
<td>2.14</td>
</tr>
<tr>
<td></td>
<td>Negative Affect (entry)</td>
<td>0.59</td>
<td>0.32</td>
<td>0.26</td>
<td>2.27</td>
</tr>
<tr>
<td></td>
<td>Fatigue (entry)</td>
<td>-1.54</td>
<td>-0.17</td>
<td>1.37</td>
<td>-1.12</td>
</tr>
<tr>
<td></td>
<td>Perceived stress</td>
<td>3.03</td>
<td>0.34</td>
<td>1.44</td>
<td>2.10</td>
</tr>
<tr>
<td></td>
<td>Intercept</td>
<td>5.88</td>
<td>2.80</td>
<td>2.10</td>
<td>0.041</td>
</tr>
<tr>
<td>Positive Affect</td>
<td>Group</td>
<td>-4.40</td>
<td>-0.29</td>
<td>1.87</td>
<td>-2.35</td>
</tr>
<tr>
<td></td>
<td>Negative Affect (entry)</td>
<td>-0.13</td>
<td>-0.06</td>
<td>0.29</td>
<td>-0.45</td>
</tr>
<tr>
<td></td>
<td>Positive Affect (entry)</td>
<td>0.48</td>
<td>0.45</td>
<td>0.15</td>
<td>3.22</td>
</tr>
<tr>
<td></td>
<td>Fatigue (entry)</td>
<td>2.42</td>
<td>0.26</td>
<td>1.51</td>
<td>1.60</td>
</tr>
<tr>
<td></td>
<td>Perceived stress</td>
<td>-1.45</td>
<td>-0.15</td>
<td>1.61</td>
<td>-0.90</td>
</tr>
<tr>
<td></td>
<td>Intercept</td>
<td>10.99</td>
<td>6.55</td>
<td>1.68</td>
<td>0.100</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Group</td>
<td>0.29</td>
<td>0.14</td>
<td>0.21</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>Negative Affect (entry)</td>
<td>0.04</td>
<td>0.13</td>
<td>0.03</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>Fatigue (entry)</td>
<td>0.45</td>
<td>0.34</td>
<td>0.17</td>
<td>2.73</td>
</tr>
<tr>
<td></td>
<td>Perceived stress</td>
<td>0.47</td>
<td>0.34</td>
<td>0.17</td>
<td>2.67</td>
</tr>
<tr>
<td></td>
<td>Intercept</td>
<td>0.39</td>
<td>0.34</td>
<td>1.14</td>
<td>0.261</td>
</tr>
</tbody>
</table>

Note. Group (0 = control; 1 = stress).

Hispanic white ethnicity. Less than half reported current use of hormonal contraception (n = 15; 28%), most estimated they were in the luteal phase of their menstrual cycle (n = 35; 67%) and reported a typical range for cycle length (i.e., 28–32 days). Depressive symptoms and perceived stress were comparable to previous studies with female undergraduates and young adults (Wilson et al., 2014; Hamarat et al., 2001). Table 1 provides descriptive statistics for demographic and psychosocial data. There was a baseline imbalance between groups on several variables. Participants randomized to the P-TSST reported lower fatigue and negative affect upon arrival at Visit 2 (p’s < 0.029; in reference to their current affective state), and lower levels of perceived stress (p = .037; in reference to the past week). These three variables were included as covariates in all models. Consistent with best practices (Sugama et al., 2009), analyses with inflammatory biomarkers controlled for BMI, as well as age and ethnicity. The control group was slightly older than the stress group, $\kappa(\text{TSST}) = 1.816$, $p = .075$, and age was negatively correlated with baseline IL-6, $r = -0.329$, $p = .015$. Non-Hispanic white participants exhibited a greater increase in IL-6 compared to other ethnicities, $\kappa(\text{TSST}) = -2.716$, $p = .009$.

3.2. Manipulation check

As expected, negative affect was higher, and positive affect was lower, following the TSST compared to the P-TSST (p’s < 0.038; see Table 2). Analyses controlled for baseline affect, fatigue and perceived stress. There were no group differences in affect or fatigue at 90 or 120 min post-TSST/P-TSST (see Table 1S).

3.3. Effect of stress on IL-6

We next verified that the TSST induced greater increases in IL-6 than the P-TSST within the mediation model framework. As hypothesized, the effect of group (TSST/P-TSST) on IL-6 was positive and significant in all mediation models, indicating that the stress group had a significantly greater increase in IL-6 than the control group; controlling for ethnicity, age, BMI, perceived stress and baseline negative affect and fatigue (see Tables 3, 4, 2S and Figs. 2 and 3).

3.4. Effect of stress-induced IL-6 on reward task performance

3.4.1. PRT reward responsiveness

Mediation analysis was conducted to test the hypothesis that stress-induced inflammation would be associated with blunted reward responsiveness, as indicated by a decrease in the PRT response bias score from pre-to 90 min post-TSST/P-TSST. For this mediation model, the indirect effect was significant, $b = 0.190$, $SE_b = 0.134$, $CI_{95\%} [0.0002, 0.5591]$, indicating significant mediation. However, contrary to hypotheses, greater stress-induced inflammation was associated with an increase in response bias, indicating an increase in reward responsiveness (see Table 3).

3.4.2. EEFT reward motivation

Mediation analysis was conducted to test the hypothesis that stress-induced inflammation would decrease reward motivation on the EEFT, operationalized as a global reduction in the proportion of high effort trials chosen from Visit 1 to 120 min post-TSST/P-TSST at Visit 2. The indirect effect did not reach significance, $b = 0.032$, $SE_b = 0.022$, $CI_{95\%} [-0.001; 0.086]$, although the relationship between increases in IL-6 and change in the proportion of high effort trials, controlling for group assignment, approached significance ($b = 0.058$, $p = 0.086$; see Table 4), such that greater increases in IL-6 predicted increased choice of high effort trials. We next evaluated effects of stress-induced inflammation on change in the proportion of high effort trials chosen at each of the three levels of probability (low, medium, high). There was no evidence that stress-induced inflammation was associated with altered motivation for high or medium probability trials; however, as shown in Table 4, there was significant mediation for low probability trials, such that greater stress-induced inflammation was associated with an increase in high effort trial choice for low probability trials (indirect effect: $b = 0.037$, $SE_b = 0.024$, $CI_{95\%} [0.0005, 0.095]$).

3.4.3. EEFT reward sensitivity

A GEE model was conducted to test the hypothesis that greater stress-induced inflammation would be associated with lower reward sensitivity on the EEFT. This analysis was conducted within the stress group on EEFT data collected 120 min post-TSST. The predictor of
Table 3
Mediation Models for Response Bias on the PRT: Inflammation as a Mediator of the Relationship Between Stress and Reward Responsiveness.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Indirect effect (path b(SE) [CI])</th>
<th>Direct effect (path c(SE) [CI])</th>
<th>Total effect (path c(SE) [CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Response Bias</td>
<td>0.190(0.134) [CI (0.0002, 0.559)]</td>
<td>0.048(0.246) [CI (-0.391, 0.573)]</td>
<td>0.238(0.224) [CI (-0.154, 0.734)]</td>
</tr>
<tr>
<td>a path b(SE)</td>
<td>0.512(0.202)* [CI (0.0002, 0.059)]</td>
<td>0.370(0.203)** [CI (0.391, 0.573)]</td>
<td>0.238(0.224) [CI (-0.154, 0.734)]</td>
</tr>
</tbody>
</table>

Note. In mediation analyses, the relationships among the group (stress vs. control), mediator (ΔIL-6), and outcome (Δreward motivation) can be characterized by several paths. The c path represents the total effect, or the effect of group on the outcome. The c’ path represents the direct effect, or the effect of group on the outcome that is not transmitted by the mediator. The a path is the group effect on the mediator, the b path is the effect of the mediator on the outcome, and the product of the a and b paths (ab) represents the indirect, or mediated effect. The indirect/mediated, direct, and total effect are deemed significant if the confidence intervals do not include zero.

Abbreviations: BS SE, Bootstrapped standard errors; CI, Bootstrapped bias corrected 95% confidence intervals; SE, standard errors; IL-6, Interleukin-6
* = significant at p < .05
** = significant at p < .01

Fig. 2. Adjusted means for change in IL-6 (log transformed) from baseline to 120 min post P-TSST/T SST.

Fig. 3. Raw IL-6 values at pre and 120 min post P-TSST and TSST for all participants.

indicating that changes in reward magnitude did not predict high effort trial choice differently as a function of greater ΔIL-6. Thus, there was no evidence for a reduction in reward sensitivity using this metric.

4. Discussion

et al., 2016; Harrison et al., 2015; Eisenberger et al., 2010; Capuron et al., 2012), we hypothesized that increases in inflammation following acute psychosocial stress would be associated with decreased performance on two well-established behavioral reward tasks. However, contrary to hypotheses, we found that stress-induced inflammation increased reward responsiveness on the PRT and selectively increased reward motivation (but not reward sensitivity) on the EEERT.

In preclinical models, inducing an inflammatory response consistently produces anhedonic behavior, and, while far less studied, similar patterns have been observed in human neuroimaging studies following endotoxin, typhoid vaccine, and interferon-alpha therapy (Harrison et al., 2016; Eisenberger et al., 2010; Capuron et al., 2012). Furthermore, among individuals with depression, elevated inflammation has been linked to dysregulation in reward neural circuitry (Pelger et al., 2015). Given this background, enhanced reward responsiveness and motivation in association with the stress-induced inflammatory response was unexpected. The rapidly expanding literature on inflammation and reward suggests a complicated relationship that may vary as a function of reward dimension (e.g., motivation vs. sensitivity; Draper et al., 2018; Lasselin et al., 2016; Dantzer et al., 2014), reward type (e.g., monetary vs. social; Eisenberger et al., 2010; Inagaki et al., 2015), level of analysis (e.g., neuroimaging vs. behavior, 26), and the magnitude of the inflammatory response (e.g., endotoxin vs. vaccination; Lasselin et al., 2016; Boyle et al., 2018). In addition, effects of stress and inflammation on reward in human models have previously been examined in isolation, but stress-induced inflammation involves a different psychological and physiological experience. Psychological stress not only initiates a cascade of physiological reactions, including the delayed peripheral release of pro-inflammatory cytokines, but also induces inflammation in the brain (O’Connor et al., 2003). Whether or how this central and peripheral co-activation alters behavior is unknown. Perhaps psychosocial stress alters neural sensitivity to peripheral inflammatory signaling, for example (Anisman et al., 2002). Indeed, in a sample of healthy young men, negative mood immediately following an acute laboratory stressor was higher among participants who had received typhoid vaccine (compared to placebo) 30-min earlier (Brydon et al., 2009). Thus, source of inflammation (e.g., peripherally vs. centrally induced) could be yet another moderator of the relationship between inflammation and reward. Accumulating evidence will allow more specific and targeted hypotheses in the future regarding how inflammation shapes reward processing.

Although small, the literature consistently suggests that motivational processes are sensitive to inflammatory challenges; however, how this alteration in motivation manifests behaviorally is not well understood. Three studies have used the EEERT and all found a different pattern. The current study found stress-induced inflammation increased motivation for low probability trials, endotoxin has been shown to increase motiva-
motivation following endotoxin in a sample of healthy men. As noted previously, these varied findings may be attributable to differences in the magnitude of the inflammatory stimulus, source of inflammation, task specific variables (e.g., presence of probability cues), or the interaction of these moderaters. Participant sex is also an important variable to further interrogate given that stress (Lighthall et al., 2012) and inflammation (Moieni et al., 2015) have both been shown to alter behavior differently in women compared to men.

There was no evidence that stress-induced inflammation altered sensitivity to reward on the EEFT. This finding aligns with all three studies that have evaluated inflammation and reward sensitivity in the context of a reward motivation task (Draper et al., 2018; Lasselin et al., 2016; Boyle et al., 2018), such that sensitivity to increases in monetary reward magnitude remained preserved while motivation was altered. This suggests a fairly consistent picture, at least for monetary reward and on a behavioral level. By contrast, an inflammatory challenge has been shown to increase reactivity in reward-related brain regions in response to social reward (Inagaki et al., 2015; Muscatell et al., 2016) and decrease response to novel images (Harrison et al., 2015). Whether similar effects would be seen for non-monetary rewards on a behavioral level has yet to be tested.

While behavioral effects of stress-induced inflammation have not previously been investigated, there is a literature on stress-induced cortisol release that may inform the current results. Specifically, when dopamine release within the reward system in response to elevated glucocorticoids (Lighthall et al., 2012). Greater increases in cortisol following stress are correlated with greater increases in striatal dopamine release (Vaessen et al., 2015), which could enhance the salience of reinforcement cues during learning. Indeed, relevant to the current results, the development of PRT response bias is associated with extrastriatal dopaminergic release (Vrieze et al., 2013; Santesso et al., 2009). Furthermore, increased dopaminergic activity increased choice of low probability trials on the EEFT, which was the pattern observed in the current study (Wardle et al., 2011). Thus, increased reward responsiveness on the PRT and increased low probability choice on the EEFT could both be driven by the downstream consequence of the cortisol response to stress, or, given that endotoxin administration also increases central dopaminergic activity (Anisman et al., 2002), the inflammatory response to stress. Additional work characterizing the time course of dopamine release in association with the stress-induced inflammatory response will be required to evaluate this possibility further.

Regarding study limitations, there was a chance imbalance on several variables at baseline; however, these were controlled in analyses. Monetary compensation for the EEFT and the PRT was not immediate, which may have reduced the salience of the reward at task administration and contributed to the loss of participant data, particularly on the PRT. This left the study underpowered to implement computational analyses (Huys et al., 2013) that would have allowed us to parse the
associations between stress-induced inflammation and reward sensitivity on the EEERT. Finally, assessment of health behaviors and status was by self-report with no independent diagnostic verification (e.g., toxicology test).

Delineating the psychobiological mechanisms of reward dysregulation has the potential to inform treatment and prevention of MDD, and is also relevant for other clinical conditions that involve impaired reward processing and dysregulated inflammatory biology, such as Alzheimer’s disease, schizophrenia, and post-traumatic stress disorder. Consistent with other emerging work, our results highlight the need to assess multiple reward dimensions, dysregulation of which may warrant different pharmacological and behavioral therapeutic approaches. It will be particularly important to continue to explore whether some reward processes, such as motivation, are more sensitive to fluctuations in inflammation than others, such as sensitivity. Examination of diverse reward stimuli beyond monetary incentive, particularly social reward (Inagaki et al., 2015), is needed.

Finally, our demonstration of detectable behavioral changes in response to the delayed inflammatory response to stress indicates this is a feasible method that can be added to the repertoire for studying affective and behavioral responses to inflammation. This method should be further interrogated given that it may capture the normative physiological changes that repeatedly occur across the lifetime in response to stressors and potentially precipitate the transition to psychopathology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2019.09.023.

References


