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The role of inflammation in acute psychosocial stress-induced modulation of reward processing in healthy female adults

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ABSTRACT

Background: Anhedonia, or loss of interest and pleasure, is a pernicious symptom of depression that involves deficits in reward processing. Stress-induced inflammation is a plausible biopsychosocial mechanism of reward deficits, but little is known whether stress-induced inflammation alters reward behavior. The present study (a secondary analysis of a completed randomized controlled trial) tested whether acute stress activated a key pro-inflammatory transcription control pathway, NF-κB, and whether this activation was associated with acute stress-induced modulation of reward processing.

Methods: Healthy female adults (age 18–25) were randomized to undergo an acute psychosocial stressor (Trier Social Stress Test; $n = 36$) or a no-stress active control ($n = 16$). The Probabilistic Reward Task (PRT) ($n = 30$ stress; $n = 12$ control) was administered at baseline and at 90 min post-stress, coinciding with the peak of the stress-induced inflammatory response. Genome-wide expression profiling and bioinformatics analyses of NF-kB transcription factor activity were used to assess pro-inflammatory gene regulation.

Results: Relative to the control condition, stress increased bioinformatic measures of NF-κB transcription factor activity ($p = .01$) and increased reward response bias scores on the PRT ($p = .03$). Within the stress condition, greater NF-κB activity was associated with greater increases in PRT scores ($p = .01$), whereas in the control condition greater NF-κB activity was associated with decreases in PRT scores ($p = .002$).

Conclusions: Acute stress increases inflammatory signaling, and this effect is associated with increased reward processing. This demonstrates the reward system to be highly sensitive to inflammatory signaling, including the relatively mild alterations that occur following a single episode of acute psychosocial stress.

1. Introduction

Anhedonia, or loss of interest or pleasure, remains a pernicious and difficult to treat symptom of depression. In addition to its association with greater severity of depressive symptoms (Gabbay et al., 2015), poorer psychosocial function (Vinckier et al., 2017), and elevated risk for disability, death (Davidson et al., 2010; Nefs et al., 2016; Covinsky et al., 2014), and suicide (Ducasse et al., 2018; Winer et al., 2014), anhedonia is less successfully treated than other symptoms of depression (Höflich et al., 2019). In order to develop effective prevention and treatment strategies, an understanding of the mechanisms that give rise to anhedonia is needed.

There is compelling evidence that elevated inflammation contributes to anhedonia. In individuals with depression, elevated markers of inflammation have been linked to anhedonia and dysregulated reward neurocircuitry (Felger et al., 2016). Administration of endotoxin, interferon (IFN)-α therapy, and typhoid vaccination induce release of proinflammatory mediators such as interleukin-6 (IL-6) and blunt neural reactivity to monetary reward (Capuron, 2012; Eisenberger et al., 2010; Harrison et al., 2016) and reduce willingness to work for monetary reward (Draper et al., 2018). One of the most relevant biobehavioral sources of elevated inflammation for psychiatric conditions is stress

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(Slavich and Irwin, 2014). Stress is a strong predictor of depression onset and has been specifically linked to anhedonia and blunted neural and behavioral responses to reward (primarily monetary reward) (Lapate et al., 2014; Pizzagalli et al., 2007; Ethridge et al., 2018; Treadway et al., 2013). Moreover, animal models have demonstrated that inflammatory signaling mediates the effect of stress on reduced reward sensitivity (e.g., reduced preference for sucrose) (Koo and Duman, 2008). This preclinical work suggests that stress-induced inflammation may be a key biobehavioral pathway to anhedonia.

A widely used method to examine the influence of stress and related pathways on behavioral responses in humans involves the use of acute laboratory stress. Many studies have used this approach to look at stress effects on behavioral measures of reward (van Leeuwen et al., 2019; Schwabe and Wolf, 2010; Petzold et al., 2010; Lighthall et al., 2013; Kruse et al., 2018; Lemmens et al., 2011; Ehlers and Todd, 2017; Berghorst et al., 2013; Bogdan and Pizzagalli, 2006) (primarily monetary reward), but little is known about inflammation as a mediator. In humans, the peak of the peripheral inflammatory response to acute psychosocial stress in humans is approximately 90–120 min post-stress (as measured by circulating cytokines) (Marsland et al., 2017; Boyle et al., 2020). Hence, administration of behavioral reward testing at 90 min post stress coincides with the typical peak increase in circulating levels of IL-6. Using this approach in adult females, we have previously shown that greater acute stress-induced increases in IL-6 were associated with increased reward responsivity (defined in prior work as the ability to modulate behavior as a function of past reward (Bogdan and Pizzagalli, 2006)) on a probabilistic reward task that was administered at baseline and at 90 min post-stress (Boyle et al., 2020). To our knowledge, this is the only study to have experimentally modeled the full biopsychosocial pathway of acute stress-induced inflammatory signaling and its effects on the reward system in humans within the same session.

A facilitative effect of acute stress-induced inflammation was contrary to hypotheses in the parent trial (Boyle et al., 2020) but was not without precedent. Indeed, studies have found largely mixed effects of both acute stress (van Leeuwen et al., 2019; Lighthall et al., 2013; Berghorst et al., 2013; Bogdan and Pizzagalli, 2006; Kumar et al., 2014) and acute inflammatory challenge (Muscatell et al., 2016; Inagaki et al., 2015; Lasselin et al., 2017) on reward processing in humans, such that stress and inflammation can each facilitate or blunt reward processing as a function of individual or methodological differences. In terms of stress, the timing of reward assessment relative to stressor onset/offset is of importance due to the temporal profile of the physiological stress response, which helps determine which systems are primarily driving behavioral changes (with the sympathetic and neuroendocrine systems receiving the greatest empirical attention). In terms of inflammation, acute inflammatory challenge (independent of stress) induces an adaptive shift towards more strategic behavior rather than an invariable anhedonic withdrawal from the environment (Irwin and Eisenberger, 2017). This recalibration has been shown to involve an increased response to environmental cues, including reward cues, so as to conserve resources and facilitate healing (Irwin and Eisenberger, 2017).

Our work similarly suggests that stress-induced inflammation increases reward responsivity, which contributes to the mixed literature on the effects of stress, inflammation, and stress-induced inflammation on reward. There is now a need for convergent evidence from other measures of inflammatory signaling. This is because increases in circulating levels of IL-6 following stress do not exclusively result from de-novo synthesis in immune cells. Instead, IL-6 is also produced and released from adipose cells (Qing et al., 2020). Moreover, a greater acute stress-induced peripheral IL-6 response could be serving as a proxy measure of greater activation and subsequent recovery of other stress signaling pathways. As one example, an enhanced reward response could result from increased dopaminergic activity in response to stressor offset (i.e., relief) or from the acute cortisol response to stress (which has been associated with increased dopamine release in reward neurocircuitry (Pruessner et al., 2004; Vaessen et al., 2015)).

Thus, the purpose of the current study is to interrogate the underlying molecular mechanisms that may be associated with acute stress-induced modulation of the reward system using data from the same parent trial (Boyle et al., 2020). Genome-wide expression profiling of mRNA from blood samples collected at baseline and 60 min post-stress (vs. non-stress control) was performed to test whether acute stress activated a key pro-inflammatory transcription control pathway, NF-κB (Hypothesis 1). Stress-induced increases in the expression of genes bearing response elements for NF-κB were hypothesized to be associated with stress-induced increases in reward responsivity on the PRT, with no such association in the control condition (Hypothesis 2).

2. Methods and materials

2.1. Participants and procedure

A total of 57 healthy female adults completed the study; the current report is a secondary analysis of a completed randomized controlled trial (clinical trials #NCT03828604). Participants were recruited May–December 2017 through the University of California-Los Angeles (UCLA) psychology department participant pool and flyers posted on the university campus. Inclusion criteria were English fluency, age 18–28, and female sex. Female sex was of interest because it is associated with heightened risk of depression and neural sensitivity to experimental inflammatory challenge (Moieni et al., 2019). Exclusion criteria included current illness, major medical conditions, current/past alcohol use disorder, pregnancy, and use of tobacco or immune-altering medications. A total of 115 participants were assessed, 69 were eligible and randomized, and 57 provided blood samples and behavioral data. Fifty-four individuals provided viable blood samples at both time points (samples yielding <4.5 M reads were excluded; $n = 1$ stress; $n = 2$ control). One individual was excluded due to acute illness during the experimental session and one was excluded due to a previously undisclosed history of cancer treatment, leaving 52 participants with useable data ($n = 36$ stress). Of these, 42 provided valid PRT data ($n = 30$ stress). See Supplementary Material, Fig. 1S, for a consort diagram. Participants also completed an additional reward task (the Effort Expenditure for Rewards Task) reported on previously (Boyle et al., 2020); results for that task are provided in Supplementary Material because there was no main effect of stress on task performance.

Study procedures have been reported elsewhere (Boyle et al., 2020) but are summarized here. After providing informed consent, participants completed questionnaires and behavioral tasks not relevant to the current report during a baseline visit. Participants were randomized 3:1 to the stress and control group via a computerized random number generator. Within approximately two weeks, participants returned for a second visit, held at the UCLA Clinical and Translational Research Center. This visit lasted 3.5–4 h and was scheduled in the afternoon to control for diurnal variation in inflammatory markers and reward processing. Participants were instructed to refrain from exercising, eating, or drinking anything except water the hour prior to this visit. Upon arrival, a nurse inserted an intravenous catheter in the antecubital vein of the participant's non-dominant arm. Participants then completed self-report measures and a baseline assessment of the Probabilistic Reward Task (PRT) (Pizzagalli et al., 2005), described below. After this, they provided the first blood sample prior to undergoing the Trier Social Stress Task (TSST) or a placebo control task (Placebo (P)-TSST) (Het et al., 2009). The TSST reliably activates the psychological and physiological stress response 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. The P-TSST has no evaluators and includes a 5-min speaking task on a neutral topic and a 5-min counting task. After the TSST/P-TSST, participants watched a neutral movie until the PRT was re-administered at 90 min post-TSST/P-TSST, to coincide with the peak of the stress-induced

inflammatory response. Blood samples for gene expression analyses were collected before and 60 min after the TSST/P-TSST.

Participants were compensated with course credit or $50. Reward task performance was incentivized with money that participants received after Visit 2[a]. All study procedures were approved by the UCLA Institutional Review Board (IRB); clinical trials #NCT03828604. Primary study outcomes for this study have been published, including main effects of stress on the PRT in a slightly larger sample (Boyle et al., 2020). None of the current data on gene expression have been previously published.

2.2. Measures

2.2.1. Inflammation

Blood samples for gene expression were collected by venipuncture in PAXgene Blood RNA tubes at baseline and 60-min post-TSST/P-TSST (prior to the peak increases in IL-6 at 90–120 min post-TSST/P-TSST (Boyle et al., 2020)). Prior work has shown an earlier peak for stress-induced changes in pro-inflammatory genes than circulating IL-6, with significant increases in pro-inflammatory genes evident at 30 min post stress and maintained at 75 min (Brydon et al., 2005). All samples were stored upright at room temperature for 24-hrs, then frozen for 24-hrs at −20C before transfer into storage at −80 °C. Samples were held in storage for 2 years. Three samples yielded marginal or poor reads at one or more timepoints (<4.5M) and were excluded. RNA extracted from blood samples was checked for suitable mass and integrity and assayed by RNA sequencing in the UCLA Neuroscience Genomics Core Laboratory using Lexogen QuantSeq 3′ FWD cDNA library synthesis and multiplex DNA sequencing on an Illumina HiSeq 4000 instrument with single-strand 65-nucleotide sequence reads, all following manufacturers' standard protocols. Sequencing yielded an average 13.2 million sequence reads per sample, each of which was mapped to the RefSeq human genome sequence using the STAR aligner (40), initially quantified as gene transcript counts per million mapped reads and then quantile normalized to reduce spurious variability and log2-transformed to reduce heteroscedasticity prior to statistical analyses.

2.2.2. Probabilistic Reward Task (PRT)

The PRT is a 15-min computerized task derived from signal detection theory which uses an asymmetric (3:1) pseudo-randomized reinforcement schedule to induce an implicit response bias towards one of two ambiguous stimuli (long and short mouths or long and short noses) (Pizzagalli et al., 2005). Because the development of this response bias relies both on reward learning (i.e., associating stimuli with rewards) and 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*. For the current study, the total response bias score was calculated across each of 200 trials at baseline and at 90 min post-TSST/P-TSST. Half of the participants completed one version of the PRT at study entry (in which the ambiguous stimuli were mouths) and a second version (in which the ambiguous stimuli were noses); the order was reversed for the other half of participants.

As reported previously (Boyle et al., 2020), 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); fewer than 16 outliers (after log transformation, trials with reaction times falling outside the mean ± 3 standard deviations were considered outliers). Ten participants were excluded, leaving a total of 42 participants ($n = 30$ stress).

2.2.3. Psychosocial measures

To test for baseline group differences, participants completed measures of depressive symptoms (20-item Center for Epidemiologic Studies-Depression scale (Radloff, 1977); possible range 0–60), and perceived stress (10-item Perceived Stress Scale (Cohen et al., 1983); possible range 0–40) prior to completing the baseline PRT. As previously reported, participants completed measures of state negative and positive affect using items from the Positive and Negative Affect Schedule (Clark and Watson, 1994) prior to and immediately after the TSST/P-TSST to assess affective response to the stress manipulation.

2.3. Analytic approach

Analyses were conducted using Stata version 13.1. Independent samples t-tests were used to test for baseline differences between the TSST and P-TSST groups. Multiple regression was used to test for group differences in affective response and reward responsivity on the Probabilistic Reward Task following the TSST/P-TSST. Models that evaluated the effect of stress used a binary predictor variable coded as 0 (P-TSST) and 1 (TSST).

To evaluate whether stress was associated with changes in bioinformatically inferred activity of the pro-inflammatory transcription factor, NF-κB (using the TELiS promoter-based bioinformatics system (Cole et al., 2005)), transcriptome-wide analyses took as input all 2367 gene transcripts showing >2-fold change in expression in association with the effect of the TSST relative to the P-TSST (Hypothesis 1). A fold-based threshold (rather than a p-value based threshold) was used because prior studies have shown this to yield superior reliability of bioinformatics results (Cole et al., 2003; Shi et al., 2008; Witten and Tibshiran, 2007; Norris and Kahn, 2006). The 2-fold threshold for candidate genes is conservative but was selected given the large number of gene transcripts (>2000) showing >2-fold differential change over time.

NF-κB activity was assessed using the V$NFKB_Q6 Transfac transcription-factor binding motif weight matrix. The log-ratio of transcription factor-binding motifs (TFBM) in the promoter sequences of up vs. down-regulated genes was assessed with results averaged over 9 parametric combinations of 3 promoter sequences lengths (300, 600, 1200) and 3 stringencies for motif detection (Transfac mat_sim values ≥ 0.80, 0.90, and 0.95) and standard errors derived by bootstrapping.

To test the association between change in pro-inflammatory gene expression and change in reward processing following acute psychosocial stress, transcriptome-wide analyses took as all input all gene transcripts showing >2-fold change in expression in association with a 1 standard deviation change in PRT response bias within the TSST group. Change in PRT reward responsivity was operationalized as change in the total response bias score, calculated by subtracting pre from post-TSST/P-TSST scores. Pre and post PRT response bias scores were z transformed prior to calculating the change score. This analysis was repeated within the P-TSST control group to evaluate the specificity of any found association to acute psychosocial stress. NF-κB activity was assessed using the same V$NFKB_Q6 Transfac transcription-factor binding motif weight matrix.

3. Results

3.1. Participant characteristics

Participants were on average 20 years old and of Latina, Asian, or Non-Hispanic white ethnicity. Depressive symptoms and perceived stress were comparable to previous studies with similar samples (Hamarat and Thompson, 2001; Wilson et al., 2014). Demographic and psychosocial descriptive statistics are provided in supplementary material (Table 1S). There were no group differences in age, BMI, race/-ethnicity, depressive symptoms, perceived stress, drinking history, or use of hormonal contraception (all p's > .05). As previously reported (Boyle et al., 2020), negative affect was higher, and positive affect was lower, following the TSST compared to the P-TSST, controlling for

[a] The IRB did not allow immediate compensation.

baseline levels of affect (all p's < 0.02 within the full sample and the subsample of PRT participants).

3.2. Manipulation check: effect of TSST vs. P-TSST on PRT reward responsivity

Consistent with results from our previous report (Boyle et al., 2020), PRT response bias scores were higher in the TSST group relative to the P-TSST at 90 min post-TSST/P-TSST, adjusting for baseline response bias scores, $b = 0.45$, SE $= 0.20$, $p = .03$, $\beta = 0.29$. Follow-up analyses indicated that there was a trend for the P-TSST group to show a decrease in PRT response bias scores, $b = -.24$, $SE = 0.17$, $p = .16$. By contrast, there was a trend for the TSST group to show an increase in PRT response bias scores, $b = .21$, $SE = 0.11$, $p = .06$. At baseline, PRT scores did not significantly differ between the P-TSST ($M = 0.27$, $SE = 0.09$) and TSST groups ($M = 0.36$, $SE = 0.08$), $t(40) = 0.65$, $p = .52$. At 90 min post-TSST/P-TSST, the TSST group had a significantly higher PRT response bias score ($M = .54$, $SE = 12$) relative to the P-TSST group ($M = 0.10$, $SE = 0.06$), $t(40) = 2.28$, $p = .03$. Change scores per each group are plotted in Fig. 2S.

3.3. Hypothesis 1: effect of the TSST vs. P-TSST on pro-inflammatory gene expression

TELiS bioinformatics analysis of all genes that empirically demonstrated > 2-fold differential change over time in average expression in the TSST relative to the P-TSST indicated increased activity of the NF-κB transcription factor in association with acute psychosocial stress (1.36-fold ratio of binding sites in up-vs down-regulated genes; $\log_2$ ratio $= 0.45 \pm 0.10$ SE; $p = .012$). Thus, as shown in Fig. 1, stress increased bioinformatic measures of NF-κB transcription factor activity. Analyses adjusting for covariates (e.g., age, body mass index, race, perceived stress, menstrual phase) were similar (see Supplementary Material).

3.4. Hypothesis 2: association between TSST-induced changes in PRT reward responsiveness and genome wide transcriptional profiling

To evaluate whether TSST-induced increases in pro-inflammatory signaling were associated with TSST-induced increases in reward responsivity on the PRT, we conducted genome wide transcriptional profiling of all genes that empirically showed >2-fold change in association with a 1 standard deviation change in PRT response bias within the TSST group. Consistent with hypotheses, increases in reward responsivity on the PRT were associated with significantly greater activity of the NF-κB pro-inflammatory transcription control pathway (2.05-fold ratio of binding sites in up-vs down-regulated genes; $\log_2$ ratio $= 1.03 \pm 0.24$ SE; $p = .012$; see Fig. 2). By contrast, within the P-TSST group, increases in reward responsivity on the PRT were associated with decreased NF-κB activity (0.66-fold ratio of binding sites in up-vs down-regulated genes; $\log_2$ ratio $= -0.61 \pm 0.08$ SE; $p = .002$; see Fig. 2). Thus, increases in PRT reward responsivity were positively associated with NF-κB activity in the TSST group, and negatively associated with NF-κB activity in the P-TSST group. Analyses adjusting for covariates (e.g., age, body mass index, race, perceived stress, menstrual phase) were similar but attenuated in the P-TSST group (see Supplementary Material).

4. Discussion

This study was designed to interrogate the underlying molecular mechanisms of stress-induced modulation of the reward system, and test for a central role of inflammatory signaling. In order to do so, it was first demonstrated that an acute psychosocial stress manipulation, the TSST, up-regulated activity in the pro-inflammatory transcription factor NF-κB, relative to a control condition, the P-TSST (Hypothesis 1, supported). Next, we verified that the TSST vs. P-TSST increased PRT reward responsivity (consistent with our prior report). Finally, we tested whether the magnitude of stress-induced change in pro-inflammatory gene expression within the TSST group showed any quantitative relationship to the magnitude of stress-induced changes in PRT reward responsivity (Hypothesis 2). These results showed that increased expression of genes bearing response elements for the pro-inflammatory transcription factor, NF-κB was associated with greater stress-induced increases in reward responsivity. This facilitative association was not evident within the small P-TSST control group. Thus, consistent with our prior work linking stress-induced increases in circulating levels of IL-6 to increases in PRT reward responsivity, the current study found associations between stress-induced increases in inflammatory signaling, as measured by genome-wide transcriptional profiling, and increases in reward responsivity.

In conjunction with our prior work, these results provide support at multiple levels of analysis (i.e., circulating inflammatory protein markers and changes in gene expression reflecting cellular function) that the effects of stress-induced inflammation on reward processing may be modeled in the laboratory, and suggest that such effects are facilitative (not inhibitory) in response to acute stress. Rather than an anomalous finding, the current work is consistent with a larger literature showing highly variable and context dependent effects of acute stress and acute

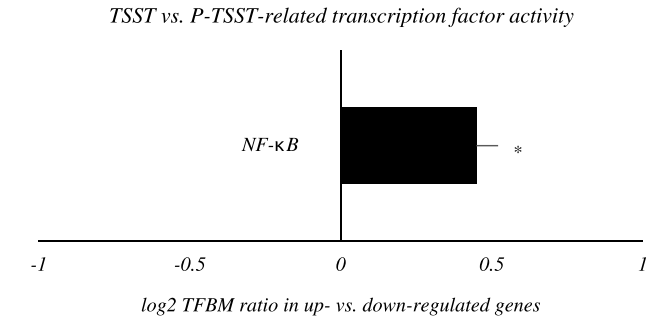

Fig. 1. Transcription factor-binding motif (TFBM) ratio for gene transcripts showing >2-fold differential change over time (pre-to 60 min post-stress) in TSST vs. P-TSST groups, as measured by TELiS promoter-based bioinformatic analyses of NF-κB TFBM in core promoter DNA sequences. Data represent log2 ratios and standard errors derived by bootstrapping.
*$p < .02$.

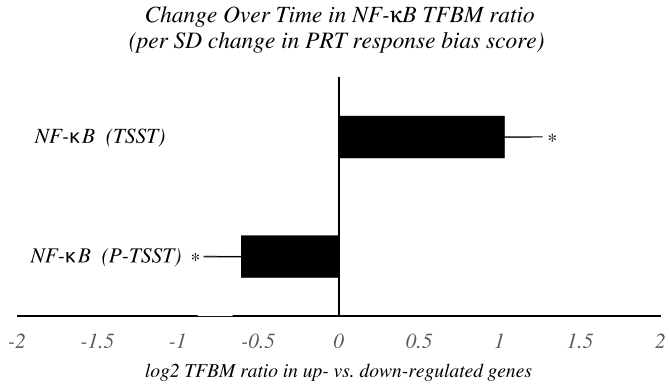

Fig. 2. Transcription factor-binding motif (TFBM) ratio for the NF-κB transcription factor, as measured by promoter-based bioinformatic analyses of all genes that showed >2 fold change over time in association with changes in PRT reward responsivity in the TSST and P-TSST. In the TSST group, increases in PRT reward responsivity were positively associated with NF-κB activity. In the P-TSST group, increases in PRT reward responsivity were negatively associated with NF-κB activity. Data represent log2 ratios and standard errors derived by bootstrapping.
*$p < .02$.

inflammation (Irwin and Eisenberger, 2017) on reward processing. This may be particularly true among healthy non-clinical participants, who mobilize resources in the context of a relatively manageable, acute stressor and respond to mild inflammatory signaling in a way that is adaptive. For example, a heightened awareness of rewards in the environment may be adaptive in terms of preparing for potential threat or illness. Moreover, it has been established that low levels of inflammatory signaling are necessary for some forms of learning and memory consolidation (Yirmiya and Goshen, 2011), and reward responsivity on the PRT encompasses both learning and sensitivity to reward components. Still, the current work is preliminary and the specific mechanisms linking increases in inflammatory signaling to behavioral change require further study.

An important next step is to test how these dynamics are altered among individuals who may be more vulnerable to experiencing stress-induced declines in reward responsivity (e.g., individuals with a history of depression or early life stress). It is not yet known if the psychological priming of psychosocial stress combined with subsequent inflammatory signaling renders at-risk individuals more likely to exhibit deficits in reward responsivity relative to healthy controls. If this were so, it would provide evidence for stress-induced inflammation as a biobehavioral pathway to anhedonia in individuals with pre-existing vulnerabilities. If this were not found, it might suggest that acute changes in inflammatory signaling are not sufficient to induce anhedonia, which may instead emerge only after long term exposure to chronically elevated inflammatory signaling.

One strength of the current study was the inclusion of a no-stress control group. Given the small size, one concern would be that any null association within the control group would be due to insufficient power rather than an indication that the effects within the TSST group were attributable to the psychosocial stress manipulation. However, the TSST and P-TSST group showed significant and differential associations with NF-κB activity; within the P-TSST group, there was an inverse association between change in reward responsivity and change in NF-κB activity (a pattern consistent with previous observations that chronic stress is associated with decreased reward responsivity and anhedonia). Given that the P-TSST group tended to show a decline in PRT response bias scores (versus the increase within the TSST group), this inverse association might be interpreted as indicating that increases in NF-κB activity were associated with decreases in reward responsivity. Although in need of replication and further study, it is possible that the variability being picked up by the control group is attributable to a subset of individuals who are highly stress sensitive (i.e., who perceived either the P-TSST or the novel environment as stressful) and exhibit subsequent declines in reward responsivity in association with changes in NF-κB activity, consistent with patterns observed in the context of chronic inflammation or chronic stress. Indeed, other work with healthy female participants has shown that stress-induced increases in IL-6 in one laboratory session were associated with decreased ventral striatal response during reinforcement learning at a separate laboratory session (Treadway et al., 2017). The immediate effects of acute stress, conversely, seem to invert the association observed under basal conditions as a function of individual differences, potentially via effects of stress on neurotransmitters in the central nervous system that alter reward system sensitivity to inflammatory signaling molecules. Replication with a larger sample size is needed to further explore this possibility.

The convergence of measures in the current study increases confidence in this laboratory model of responsivity to stress-induced inflammation. At the same time, it is important to note that increases in circulating plasma protein markers such as IL-6 are not expected to necessarily correlate with changes in gene expression (which represent changes in circulating leukocyte abundance and/or function). Increases in circulating levels of IL-6 result from numerous stress-related changes beyond de-novo synthesis in immune cells. For example, acute stress increases production of IL-6 in brown adipocytes (Qing et al., 2020), and existing IL-6 in adipose tissue or lymphoid organs is released into circulation following stress. Thus, while the current study reports on NF-κB transcription factor activity in circulating leukocytes, our previous analyses of plasma IL-6 most likely reflect cytokine production in adipose and other solid tissue sources. Circulating levels of IL-6 are also closely regulated by the neuroendocrine response; for example, animals that are adrenalectomized show attenuated stress-induced increase in IL-6 (Zhou et al., 1993). By contrast, changes in pro-inflammatory gene expression in circulating leukocytes are by definition highly localized and more dependent on beta-adrenergic signaling. For example, administration of beta-adrenergic antagonists such as propranolol attenuates stress-induced increases in pro-inflammatory gene expression but does not alter stress-induced release of IL-6 (MacCormack et al., 2021). Thus, rather than solely representing a precursor to circulating proteins, gene expression represents a distinct inflammatory process that works in coordination with circulating levels of IL-6 to alter inflammatory signaling. This study confirms that cellular measures of inflammatory activity show similar relations to acute stress and reward system activation as previously observed for the plasma protein marker IL-6.

Regarding study limitations, the sample size is small for individual differences research. This is particularly the case for the P-TSST group. While small, the P-TSST control group was stringent and enabled us to focus on the effect of social evaluative threat in the TSST rather than effects due to general arousal or cognitive load. Standard data cleaning resulted in a loss of participant data for the PRT. This smaller sample size raises some concern about the generalizability of the data. However, the group difference in change in PRT scores was similar, if attenuated, when including all participant data. Assessment of health behaviors and status was by self-report with no independent diagnostic verification (e.g., toxicology test). Another limitation is the focus on a single reward task, which means that other domains of reward (e.g., motivation) and other types of reward (e.g., social reward) were not explored, nor was sensitivity to punishment or loss. This study involved a sample of healthy young women, and the generalizability of these results to other populations remains to be determined in future studies. Finally, several alternative explanations for study results cannot be ruled out. For example, the affective response to the stress manipulation could serve as a third variable that separately induced both an increase in inflammatory signaling and an increase in reward responsivity (e.g., as a relief response, or compensatory efforts to modulate mood following a stress challenge). However, the likelihood of this mechanism is reduced with the current study design, in which behavioral testing occurred 90 min following the stressor (at which point the TSST and P-TSST groups did not show a difference in affect or fatigue (Boyle et al., 2020)). Alternative biological explanations include stress-induced increases in cortisol, which are known to be correlated with increases in striatal dopamine release (Vaessen et al., 2015); additional work is needed to determine whether the time course of this mechanism could explain results in the current study. Finally, while mediation analysis would have been an ideal approach for the conceptual model proposed in this study, bioinformatic analysis of NF-κB activity derives from lists of differentially genes and thus does not generate any individual-specific NF-κB activity level estimates that could be used in mediation analyses. Direct, individual-specific measures of NF-κB activity are an opportunity for future research studies.

Using genome wide transcriptional profiling and bioinformatics analysis, the current study demonstrated that an acute psychosocial stressor, the TSST, increased bioinformatic measures of NF-κB transcription factor activity (baseline to 60 min post stress) and had delayed facilitative effects on reward responsivity (baseline to 90 min post stressor). Moreover, these delayed facilitative effects of stress on reward responsivity were associated with increased activity of NF-κB, suggesting that inflammatory activation represents a key molecular mechanism of acute stress-induced modulation of the reward system. These results are consistent with a large body of literature showing that stress and inflammation independently modulate the reward system and extend

the literature by providing a preliminary test of the effects of stress-induced inflammation. A critical question going forward is whether these findings can be leveraged to study the chronic dynamics relevant to anhedonia or can inform our understanding of anhedonia. Specifically, if the reward system is so keenly attuned to the inflammatory signaling that occurs in the aftermath of acute stress, it may be particularly vulnerable to repeated experiences of stress or the effects of more sustained elevations in inflammation, as can occur in the context of acute or chronic illness.

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2023.100588.

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