Stress, Inflammation, and Well-Being
Study Protocol
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BACKGROUND AND PROTOCOL SUMMARY

Summary

In this study we propose to examine the association between psychosocial stress, the stress-induced inflammatory response, and reward processing in a female undergraduate sample. Specifically, we will 1) examine effects of an acute psychosocial stressor on reward processing; 2) evaluate the association between stress-related changes in inflammation and reward processing; and 3) test key vulnerability factors that may moderate the association between stress and reward. To achieve these goals, this study will recruit 60 female undergraduate students to test effects of stress on reward processing in a 3.5 hour laboratory session. Participants will be randomly assigned to either experience a laboratory stressor or a placebo control (Het et al., 2009), and will complete reward tasks 90 minutes post stress/placebo onset, at which point the peripheral inflammatory response to stress reaches its peak (Kuebler et al., 2015). The reward tasks are computerized behavioral tasks that assess three domains of reward processing: reward-learning, reward motivation, and reward sensitivity. Throughout the session, all participants will complete self-report measures of affect and provide blood and saliva samples for evaluation of the psychological and physiological stress response. Within one week prior to the session, participants will attend a 1 hour visit in which they complete baseline reward tasks and self-report questionnaires assessing mood, personality, early life stress, and health behaviors. In total, participants will complete two visits, with a duration of 4.5 hours. This study builds upon prior studies demonstrating immediate effects of acute stress on reward processing, and further tests for delayed effects of acute stress on reward processing. Furthermore, this will be the first study to examine inflammation as a mechanism linking stress to deficits in reward processing. Findings may inform theory of depression etiology and contribute to more specialized treatment that is targeted at specific symptoms of depression.

1. Introduction and rationale

Major depressive disorder (MDD) is debilitating, chronic, and widespread, with a lifetime prevalence of 16.2% for United States adults (Kessler, Merikangas, & Wang, 2007). The etiology and best treatment for MDD remains poorly understood, likely because clinical presentation of MDD is enormously heterogeneous. As such, research in psychopathology has begun to shift towards a dimensional approach in the study of mental illness, with a focus on fundamental psychological and biological processes rather than diagnostic categories (Insel et al., 2010; Miller & Rockstroh, 2013). One dimension receiving increasing attention is reward processing, impairments of which are associated with anhedonia. Most commonly defined in research as "an inability or reduced ability to experience pleasure", anhedonia actually reflects a broad array of potential deficits in reward-related processes, including the ability to learn from, respond to, and motivate oneself towards reinforcing stimuli.

Anhedonia is of particular interest in depression research for several reasons. In addition to its role as a key diagnostic symptom, there is evidence that anhedonia precedes the onset of depression and persists after

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depressive episode remission, suggesting that anhedonia may be a trait vulnerability contributing to onset and/or recurrence of depression (Hasler et al., 2004; Pizzagalli, 2014). For example, reward-related learning, measured as a tendency to develop a response bias towards rewarding stimuli, shows heritability and stability over time, and remains impaired in individuals currently in remission from MDD (Goldstein & Klein, 2014). Similarly, non-symptomatic healthy individuals higher in self-reported anhedonia exhibit subclinical neural and behavioral symptoms of depression, such as decreased neural reactivity in response to pleasurable stimuli in the ventral striatum, a brain region associated with reward functioning (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005).

Recent work has proposed a central role for stress in the relationship between reward processing and depression. Specifically, the induction of anhedonia through stress has been theorized to precipitate depression (Pizzagalli, 2014). Strong evidence in animal models, and preliminary evidence in human models, indicates that chronic and acute stress alters reward processing (Gold, 2015). In human studies, individuals with higher perceived stress and depressive symptoms show blunted reward-learning (Treadway et al., 2013; Pizzagalli et al., 2007), and experimental work has shown that acute stress blunts reward-related learning to a similar degree in healthy individuals (Bogdan & Pizzagalli, 2006). However, mechanisms linking stress, reward, and depression have not been determined.

Converging evidence suggests that stress-related alterations in inflammatory biology may be a key mechanism. There is a substantial literature linking elevated inflammation to symptoms of depression, such as fatigue, social withdrawal, and anhedonia (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Eisenberger et al., 2010; Slavich & Irwin, 2014), including studies that demonstrate that inflammation experimentally elicited through typhoid vaccine can induce alterations in reward-learning (Harrison et al., 2015). Indeed, inflammation has been theorized to be a central pathway by which stress is transduced into depressive symptomatology (Slavich & Irwin, 2014). In animal models, inflammation has been shown to mediate the link between stress and anhedonic symptoms (Koo & Duman, 2008), but no studies have tested whether stress-induced inflammation influences reward processing in humans.

Thus, the purpose of this study is to integrate findings from two key bodies of literature that have yet to be bridged: one suggesting that stress-induced anhedonia precipitates depression (Pizzagalli, 2014) and one suggesting that psychosocial stress-induced inflammation contributes to depression (Slavich & Irwin, 2014), by examining the effects of an acute psychosocial stressor on reward processing and the possible role of inflammation within these dynamics.

Acute stress will be manipulated using a common psychosocial stress paradigm, the Trier Social Stress Task (TSST; Kirschbaum, 1993). Multiple facets of reward processing will be assessed to examine whether stress and/or inflammation is particularly influential in any given domain of reward processing, including reward motivation, reward learning, and reward sensitivity. Results from this study will advance our understanding of depression etiology by helping to clarify the nature of the well-documented association between stress and depression, and contribute to more targeted and individualized treatment for a highly heterogeneous and devastating disorder.

Specific Aims and Hypotheses

Aim 1: To examine effects of stress-induced inflammation on three domains of reward processing: reward learning, reward motivation, reward sensitivity. We hypothesize that increases in IL-6 following acute stress will predict decreased reward learning, motivation and sensitivity 90-120 minutes post stress.

Aim 2: To test key vulnerability factors that may moderate the association between stress-induced inflammation and reward. We hypothesize that individuals with a) a history of early adversity, b) current depressive

symptoms, or c) high trait anhedonia will evidence greater decrements in each of the three indices of reward processing in association with the stress-induced inflammatory response.

Aim 3: To test whether the degree of reward dysregulation in response to stress-induced inflammation will predict increases in depressive symptoms and perceived stress, and decreases in positive affect, four months following the experimental session.

2. Summary of Research Protocols

Participants. Participants will be biologically female, age 18-28 and fluent in English. Most will be UCLA undergraduate students recruited through the UCLA SONA system, although we will expand recruitment to the greater UCLA campus and surrounding neighborhood if necessary. A female sample will be recruited because stress effects on reward processing differ by gender (Lighthall et al., 2012), depressive symptoms and inflammation-related disorders are more prevalent among women (Slavich & Irwin, 2014) and previous work has shown correlations between the inflammatory response to endotoxin in females but not males (Moieni et al., 2015). In addition, we will recruit 10 male UCLA undergraduate students for comparison purposes if funding permits. Compensation will be credit through the UCLA SONA system, or $50 for those not participating through SONA. Those who complete a 4-month follow-up survey will receive money derived from their performance on three of the reward processing tasks.

Summary of Procedures. Study participation involves two visits. Visit 1 requires participants to come to the Mind-Body Laboratory for 1 hour. At this time we will obtain informed consent, and the participant will complete questionnaires and reward tasks. Visit 2 will be one laboratory visit that will last 3.5 hours. For Visit 2, participants will be scheduled for an afternoon session to account for diurnal rhythms of cortisol. A research assistant will meet the participant at the Mind-Body Laboratory and walk them down to the Clinical and Translational Research Center (CTRC) at UCLA. Upon arrival, a nurse will take vitals and insert an intravenous catheter in the antecubital vein of the non-dominant arm for blood draws. Participants will complete questionnaires and computerized behavioral reward tasks, and then undergo an acute 15 minute laboratory psychosocial stressor, the Trier Social Stress Task (TSST), or a placebo control. They will then watch an emotionally neutral documentary video until 90 minutes post-stress onset, at which point participants will again complete behavioral reward tasks. Throughout the session, participants will provide saliva samples for analysis of cortisol reactivity and recovery (9 times), blood samples for analysis of immune activation (4 times), and self-report measures of affect for analysis of the psychological stress response (seven times). Blood pressure and heart will be assessed along with each cortisol assessment. At 200 minutes post-arrival, participants will be debriefed.

STUDY PROTOCOL

1. Subject recruitment, protocol assignment, and eligibility evaluation

1.1 Recruitment of participants

Participants will be undergraduate students recruited through the UCLA SONA system and compensated for their participation with 5 hours' worth of course credit. Participants will be told the experiment involves a 3.5 hour session that includes providing blood and saliva samples, assessment of blood pressure and heart rate, completion of behavioral tasks, a challenge task, and self-report questionnaires, and an additional 1 hour session that includes completing behavioral tasks and self-report questionnaires. Interested participants will be asked to contact the study team through a study email and then screened by phone for eligibility. Participants will also be recruited through flyers posted on the UCLA campus and surrounding neighborhood; we will recruit participants who are between the ages of 18-28, biologically female and fluent in English to match the anticipated demographics of the SONA participants. In a brief phone interview, the PI or authorized study personnel will describe the purpose of the study and level of commitment involved.

1.2 Participant inclusion and exclusion criteria

Inclusion criteria. Participants will be biologically female, age 18-28 and fluent in English. Given that stress effects on reward processing differ by gender (Lighthall et al., 2012), that depressive symptoms and inflammation related disorders are more prevalent among women (Slavich & Irwin, 2014) and that previous work has shown correlations between inflammatory markers and psychological response to endotoxin in females but not males (Moieni et al., 2015), we will restrict recruitment to a female sample. We aim to recruit an additional 10 male participants for comparison purposes if additional funding is obtained.

Exclusion criteria. Participants will be excluded for the presence of disorders with an inflammatory component, such as colitis, rheumatoid arthritis, asthma, and untreated allergies, as well as regular use of steroid medications known to influence neuroendocrine or inflammatory systems. Participants with recent or acute illness will be eligible but scheduled to participate after at least two weeks without illness. Participants who smoke or meet criteria for alcohol use disorder will be excluded. Women currently or imminently planning to become pregnant will not be eligible.

1.3 Phone Screening Evaluation

Individuals interested in participating will be asked to contact the research staff through a study email and then screened for eligibility. In a 10-15 minute phone interview, the PI/research team will describe the study and level of commitment involved. If the individual is still interested, the participant will be screened for inclusion/exclusion criteria. The PI will then review the screening to determine if screening for alcohol use disorder is warranted. If the participant meets criteria for alcohol use disorder, the PI will refer the participant to campus resources for treatment (UCLA Counseling and Psychological Services). If the participant is eligible, the PI will randomly assign the participant to the stress or placebo control condition using a random number generator. Participants will then complete Visit 1. For Visit 2, participants will be asked to refrain from drinking (water ok) and eating for one hour prior due to potential effects on inflammatory and HPA axis activity.

2. Laboratory Protocol

2.1 Informed Consent

During Visit 1, participants will complete the consent process. Consent will be conducted by the study PI or authorized study personnel. Consent procedures will take place at the Mind-Body Laboratory in a private room. The participant will be offered as much time as necessary to review the permission form and to ask questions before providing a signature indicating agreement to participate in the study.

**Overview of Laboratory Session**

Participants will be scheduled for Visit 1 at the Mind-Body Laboratory. Visit 1 will last 1 hour. Upon completion of the consent procedures, the participant will complete behavioral reward tasks and questionnaires and then scheduled for Visit 2. Visit 2 will be scheduled in the afternoon. Participants will be instructed to meet the research team at the Mind-Body Laboratory; a research assistant will then walk the participant down to the Clinical and Translational Research Center (CTRC) at UCLA. Upon arrival, a nurse will insert an intravenous catheter in the antecubital vein of the non-dominant arm for blood draws. The maximum amount of blood to be drawn from each participant is 90 mL, or 6 tablespoons. This is a routine medical procedure. Participants will then complete baseline questionnaires assessing recent behaviors that might influence the physiological stress response (e.g., sufficient sleep the previous night). At pre-specified intervals, participants will complete measures of state affect, self-conscious emotions, and task appraisals. Participants will then complete three behavioral reward tasks, the probabilistic reward task (PRT; 14-15 minutes) the dot probe task (5-6 minutes), and an emotion identification task (5 minutes). Participants will provide their saliva and blood samples at specific intervals (see 2.6 section below). They will next receive instructions for the Trier Social Stress Task (TSST) or for the Placebo-TSST (P-TSST). After the TSST/P-TSST, participants will watch a 60-minute emotionally neutral documentary. At 90 minutes post TSST/P-TSST onset, participants will complete the PRT, dot probe and emotion identification task for a second time (counterbalanced), an effort expenditure task for the first time (15 minutes), and a charitable giving task (administered last, 3 minutes). Administration of the tasks will take approximately 50 minutes. At 200 minutes post-arrival, participants will be debriefed.

2.2 Behavioral Reward Tasks

2.2a *Reward-related learning.* The Probabilistic Reward Task (PRT) (Pizzagalli et al., 2005) is a 14-15 minute signal-detection task that objectively measures reward-related learning. The PRT uses an asymmetric reinforcement schedule with social reward (positive feedback). In each trial, participants identify which of two difficult-to-differentiate stimuli are presented. The stimuli are cartoon faces with one of two straight mouths (10mm short mouth versus 11mm long mouth). At the beginning of a trial, the face has no mouth, and then one of the faces with the mouth is briefly presented. Participants are asked to indicate which of the two faces was presented. Unbeknownst to the participant, an asymmetrical reinforcement schedule is used to induce a response bias towards one of the faces (termed the "rich" stimulus), with one of the faces rewarded three times more frequently than the other (termed the "lean" stimulus). Both faces are presented an equal number of times. In healthy individuals, this reinforcement schedule leads to an implicit response bias favoring the more frequently rewarded stimulus; the magnitude of this response bias is used to operationalize reward learning and is used as the dependent variable in the proposed study.

The task consists of a total of 200 trials divided in two blocks. Each block lasts 7 minutes, and participants have a 30 second break in between blocks. Each trial begins with the presentation of a fixation cross in the middle of the screen [750 ms], followed by the presentation of a mouthless cartoon face [500ms] and then presentation of a face with a mouth [100 ms]. The mouthless face remains on the screen as the participant uses the keyboard to indicate whether the short or long mouth was presented. For each block, 40 correct response trials are followed by positive feedback [1500ms] ("Correct! You won 5 cents!"). If the participant is inaccurate, or accurate on a non-rewarded trial, a blank screen is displayed [1750ms]. Participants are informed that only some correct responses will be rewarded prior to the task. Because the PRT will be administered before and after the TSST/P-TSST, one administration will use mouth size stimuli, and one administration will use nose size stimuli, in order to reduce practice effects.

Example of PRT mouth stimuli

Big mouth   Little mouth
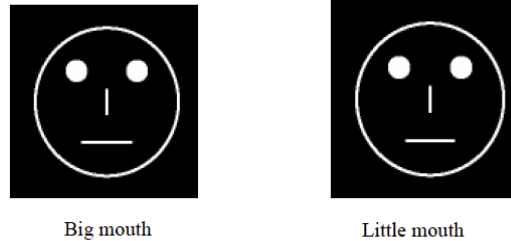
2.2b Reward Motivation. The Effort Expenditure for Rewards Task (EEfRT; Treadway & Zald, 2011) operationalizes reduced motivation for a reward as a decreased willingness to exert greater effort for higher rewards, particularly when rewards are uncertain. In the task, participants are presented with a series of trials in which they choose between a "hard-task" and an "easy task" in order to earn varying amounts of money. They win money by pressing a button a predetermined amount of times within a set time frame. Hard-task trials require the subject to make 100 button presses using the non-dominant little finger within 21 seconds. The easy-task requires 30 button presses using the dominant index finger in 7 seconds. Subjects can win $1.00 for easy-task trials. For the hard-task, participants can win a varying amount with a range of $1.24 -$4.30 (varying reward magnitude). In addition, participants are told that only some of the trials will give them a reward for a correct response. They are given probability information on whether the trial is a possible win trial or not (88%, 50%, 12%). Probability of reward and reward magnitude are manipulated to look at the conditions under which a person will exert effort for a reward. The EEfRT takes 15 minutes; participants have a 30 second break halfway through the task. Participants will be told they can win the summed amount of two randomly selected trials from the task. The amount a participant can win ranges from $2.00 to $8.24. The EEfRT will be administered at Visit 1 and after the TSST/P-TSST.

2.2c Perceptual Reward Sensitivity. A 6 minute computer based dot probe task will be used to assess for attentional bias towards positive facial stimuli. Positive social stimuli, such as happy facial expressions, are conceptualized as primary rewards that elicit approach oriented behavior (Berridge & Kringelbach, 2008; Yoon et al., 2009). The response in healthy controls is increased bias towards happy versus neutral faces, which is indexed as faster reaction time when a visual probe replaces the happy face on either the right or left side of the screen. During the task, participants are informed that they will see a dot appear on either the right or left side of the computer screen, and that their task is to respond as quickly as possible by pressing one of two keys indicating the side the dot is on. Prior to seeing the dot participants are told they will see two faces (flashed side-by-side on screen for 500 ms to allow for conscious processing of the stimuli) but do not need to respond to them. They will view a total of 40 pairs of photographs of different faces, with each pair consisting of two photographs of the same person side-by-side on the screen. One photograph is of a neutral expression, while the second is emotional (angry, sad, happy, happy-low arousal). There are 10 pairs of neutral/angry, 10 pairs of neutral/sad, 10 pairs of neutral/happy-low arousal, and 10 pairs of neutral/happy faces. Each pair is presented four times so that all possible combinations of emotional face location (left, right) and dot location (left, right) are seen. There are a total of 160 trials (all face pairs are randomized for each participant). Angry and sad faces are included to assess whether any effects of stress or inflammation on attentional bias are specific to positive stimuli. All faces will be taken from the NimStim set of facial expressions (Tottenham et al., 2009), which is in color and has a diverse set of models for each expression. The dot probe task is completed before and after the TSST/P-TSST.

2.2d. *Emotion identification task.* In the emotion identification task, participants will be presented with a picture depicting different emotions at various levels of intensity. These pictures were created by morphing photographs that display different emotions (e.g., Sad, Angry) (Pollak & Kistler, 2002). Therefore, the

photographs will vary in emotional intensity within a continuum that ranges from neutral to sad, neutral to happy, neutral to angry, or neutral to fearful. Twenty two pictures (11 males; 11 females) within each emotion pair (e.g., Neutral vs. Sad) will be presented at 10% increments of intensity of the target emotion (e.g., 0% sad, 10% sad, … 100% sad). All faces will be taken from the NimStim set of facial expressions (Tottenham et al., 2009). After the presentation of each picture, the participant will be asked to indicate which emotion the face resembled most by making a choice via a left or right button on a response box (e.g., NOTHING vs. SAD or NOTHING vs. HAPPY, etc). This task will take approximately 5 minutes and is completed before and after the TSST/P-TSST.

2.2e. *Prosocial choice and emotional reactivity.* This task will be administered at the end of Visit 2. Participants will complete a computer task that asks participants whether they would like to donate up to $10 of their potential earnings to a well known charity (e.g., American Red Cross) or a charity of their choice (Barraa, McCullough, Ahmadi, & Zak, 2011). After making their decision, participants will complete the VAS measures used throughout the session to assess affective reactivity to prosocial behavior. Participants are told this is an anonymous decision. Regardless of their choice, participants will receive their money if they respond to a subsequent questionnaire at the 4-month follow-up. The dependent variable is choice to donate (yes/no) and amount donated (continuous measure). This task will be included because charitable giving is associated with heightened reactivity in reward-related regions in the brain (Harbaugh, Mayr, & Burghart, 2007).

2.2f. *Prosocial behavior.* The Dictator Game (DG) and the Ultimatum Game (UG; Guth, Schmittberger, & Schwarze, 1982) are brief computer tasks that will be used to measures pro social decision making. In the DG, the participant is given a role (Player B) and asked to allocate money that is presented in a decision tree format to another person (Player A) and herself. The participant has the choice to allocate the money in a more or less prosocial manner (e.g., choosing an option in which both parties receive money even though the participant could otherwise receive more money). There are 6 trials. The UG is similar, but incorporates an element of risk. Across eight trials, the participant decides how to split the money with an opponent player. If the opponent rejects the offer, both parties lose the money. Fair offers are more likely to be accepted. The dependent variable is the average amount the participant proposes, with higher numbers indicating more prosocial behavior. Order of administration of the UG and DG will be counterbalanced. Total administration time is 5 minutes. The participant is told they can win up to $5 based on their performance on the games. These tasks will be administered at Visit 1 and are considered exploratory. We will test whether higher prosocial tendencies moderate the stress-induced inflammatory response.

2.3 Trier Social Stress Task (TSST) and Placebo–TSST

Following completion of pre-stress reward tasks, participants next receive instructions for the Trier Social Stress Task (TSST; Kirchbaum, 1993) or for the Placebo-TSST (P-TSST; Het et al., 2009). The TSST is a commonly used 15 minute psychosocial laboratory stressor, in which participants are asked to imagine that they are invited to an interview for a position they find desirable (e.g., research assistant position, internship) and are told that they will be delivering a five-minute speech on how they are an ideal candidate. Participants are informed that their performance will be recorded and evaluated. They are given three minutes to prepare their speech, and then deliver the speech for five minutes in front of a panel of two student research assistants who are trained to provide nonverbal negative feedback and are dressed in white laboratory coats. Participants then complete a five-minute mental arithmetic task in front of the panel in which they are asked to count backwards by 13 from 2,395 as quickly and as accurately as possible. They receive corrective feedback from the panel each time they make a mistake, and are asked to start over. The TSST reliably activates the HPA stress axis, influences immunological parameters, and leads to high levels of self-reported stress and anxiety (Frisch, Häusser, & Mojzisch, 2015; Steptoe et al., 2007). The P-TSST parallels the TSST in terms of general procedure and duration but removes social evaluative components and does not elicit a strong physiological response. In the P-TSST, participants prepare for three minutes to talk out loud about a neutral topic (e.g., describing a

recent movie or book that they have read). While in a room alone, they speak out loud for five minutes, and then count forwards by 15s, starting at 0. The P-TSST was chosen for the proposed study because it provides some control for effects of cognitive load on performance in the behavioral reward tasks (Frisch et al., 2015).

2.4 Neutral Movie

Following the TSST/P-TSST, participants will watch a neutral documentary video. The neutral video will be episodes from "How It's Made" from the Discovery Learning Channel, which describes how a number of everyday objects are manufactured, and was chosen to be both neutral and interesting. Participants watch this video for approximately 60-75 minutes. The video is stopped at 90 minutes post TSST/P-TSST onset, at which point behavioral reward tasks are administered.

2.5 Self-report questionnaires during the laboratory session

2.5a Emotional reactivity and recovery. Emotional reactivity and recovery from the TSST/P-TSST will be assessed using items from the Positive and Negative Affect Schedule (Watson & Clark, 1999; Thompson, 2007), including the negative and positive affect scales (10 items each). Additional items from the serenity subscale will be used to assess low arousal positive affect and two items will be created for this study (apathetic, numb). Participants will rate how they feel "right now (that is, at the present moment) on a 1 (very slightly or not at all) to 5 (extremely) Likert scale. These questions will be administered seven times, upon arrival, prior to the stressor, immediately post stressor, and 60, 90, 120, and 150 minutes post stress onset. This will allow us to examine effects of stress on positive and negative affect, and to determine associations between performance on behavioral tasks and emotional responses. Additional emotions relevant to feelings of fatigue will also be assessed using items from the Profile of Mood States Scale-short form (Curran, Andrykowski, & Studts, 1995). Participants will complete the fatigue (8 items) vigor (5 items) and confusion subscales (7 items) alongside the PANAS. Participants will rate how they feel "right now (that is, at the present moment) on a 1 (very slightly or not at all) to 5 (extremely) Likert scale.

Given previous work directly linking self-conscious negative emotions to the inflammatory response (Dickerson et al., 2009), participants will also complete the State Shame and Guilt Scale (Marschall, Sanftner, & Tangney, 1994) after the TSST/P-TSST. Example items include: "I want to sink into the floor and disappear"; "I feel humiliated, disgraced"; "I feel like I am a bad person" to measure guilt. Participants rate how much each statement is accurate about how they feel at the current moment on a 5-point scale ranging from not feeling this way at all (1) to feeling this way very strongly (5).

Given research showing that associations between subjective response to the TSST and stress physiology may be more detectable using visual analogue scales (VAS) during the stressor (Hellhammer & Schubert, 2012), participants will be asked to rate how stressed, anxious, angry, confident, calm, socially connected and happy they are currently feeling using a visual analogue scale alongside the PANAS and at the following additional time points: prior to speech instructions, after speech preparation, after the speech, and after the math portion of the TSST/P-TSST. Additionally, at the end of Visit 2 participants will complete a modified version of the Intrusive Thoughts subscale from the Impact of Events Scale (Horowitz, Wilner, & Alvarez, 1979) to assess the degree to which they ruminated about the TSST.

2.5b Cognitive appraisal. The Primary and Secondary Appraisal Scale (Gaab, Rohleder, Nater, & Ehlert, 2005) will be used to assess how participants evaluate the stressor. Participants rate whether they agree with statements such as "I do not feel threatened by the situation," "Whether the experts judge me positively mainly depends on me." Participants complete this task prior to the TSST/P-TSST.

2.5c *Session evaluation.* After each behavioral reward task, participants will be asked to answer questions assessing task appraisal (enjoyable, difficult, interesting; chosen to reflect emotions consistent with reward processing) on a 1 to 5 Likert scale. After completing the TSST/P-TSST, participants will complete 5 questions

assessing task impressions (e.g., "The panel was harsh in their evaluations") on a 1-7 scale, and 17 questions assessing post-task appraisals (e.g., "I did well on the tasks") on a 1-7 scale. Prior to the debriefing, participants will be asked open-ended questions about their impressions of the laboratory session.

2.6 Inflammatory and neuroendocrine response to acute stress

2.6a *Inflammation.* Participants will provide their first blood draw 45 minutes after arriving to allow for reactivity to the novel situation to subside. Subsequent blood draws will be completed 60, 90, and 120 minutes post-stress onset. Research suggests the peak of the inflammatory response following the TSST is 90 minutes post stress completion, with elevations still evident at 120 minutes (Kuebler et al., 2015). The 90-minute peak will be used in the proposed study to examine associations between inflammation and performance on behavioral reward tasks. All blood samples will be collected by venipuncture into ethylene diamine tetra-acetic acid tubes and placed on ice immediately after collection. At each of the four time points, collection will be for two 6 mL lavender tops for assessment of peripheral levels of IL-6 and one 2.5mL PAXgene tube for assessment of proinflammatory gene expression. After the study session, nursing staff will take the samples to the Pathology Research Portal for processing and storage. Samples will be centrifuged for acquisition of plasma and stored at -80°C. At study completion, samples will be taken to the UCLA Inflammatory Biology Core Laboratory and assayed for IL-6 using a high sensitivity enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, Minn). Samples will be assayed in duplicate and each subject's samples will be assayed in the same run to avoid interassay variability. Plasma and RNA samples will be stored for future assays.

2.6b *Cortisol.* Participants will provide nine saliva samples across the 3.5 hour session for assessment of cortisol reactivity and recovery. Saliva samples will be collected using Salivettes (Sarstedt, Inc) and stored at -80°C. They will be shipped to the Kirschbaum lab in Germany where they will be assayed for cortisol in duplicate using an enzyme-linked immunoabsorbent assay. Samples will be collected upon arrival, after baseline reward tasks, immediately post stressor, and 15, 30, 45, 75, 105, and 135 minutes post stressor. Heart rate and blood pressure will also be monitored at each of these time points.

2.7 Debrief

At 200 minutes post-arrival, participants will be debriefed. Participants will first answer several questions assessing their impressions of the laboratory session. Research assistants will then use a script to debrief the participant, which informs the participant that the performance of the participant was not recorded and that no analysis of the participant's speech or math performance will be conducted. Research assistants will explain that the tasks were unreasonably difficult and do not reflect upon the participant's aptitude or ability. The debriefing is modified for those who did not experience the TSST. All participants also receive a resource sheet for counseling services at UCLA.

3. Questionnaires.

Participants will be asked to complete questionnaires at Visit 1 through the online survey platform Qualtrics. Questionnaires will be administered before the experimental session to avoid carryover effects of the questionnaires on the behavioral tasks (and vice versa) during the session. Questionnaires will take approximately 30 minutes to complete. Participant will complete the questionnaires in a private room at the Mind-Body Laboratory.

Questionnaires will assess demographics, health behavior (including exercise and sleep), personality, and mental health history. These measures will be used to characterize the sample. Questionnaires will also assess trait and state anhedonia, depressive symptoms, and early life adversity. These measures will be used to examine vulnerability factors that may moderate effects of stress on reward processing.

3.1 Characterizing the sample

3.1a *Anxiety symptoms.* The 7-item Generalized Anxiety Disorder-7 will be used to assess anxiety symptoms. Prior research has shown that heightened levels of anxiety are associated with reward processing under stress (Morris & Rottenberg, 2015). Participants are asked to indicate how often during the past two weeks they have felt bothered by symptoms such as feeling on edge, worrying, and having trouble relaxing on a 0 (not at all) to 3 (nearly every day) scale.

3.1b *Personality.* Two subscales from the 24 item Eysenck Personality Questionnaire-Revised short form (EPQR-S; Eysenck & Eysenck, 1992), assessing extraversion and neuroticism, will be used to assess personality. Extraversion is associated with mesolimbic dopaminergic reward processing and it has been proposed that extraverts are more sensitive to reward than introverts (Smillie, Wacker et al., 2015). Other work suggest that neuroticism is associated with reduced neural reward processing (Kehoe, Toomey, Balsters, & Bokde, 2012). We will also administer the LOT-R to assess optimism; this trait has been posited to be associated with reward processing and underlie resilience to stress (Southwick, Vythilingam, & Charney, 2005)

3.1c *Affect.* Trait positive and negative affect will be assessed using items from the Positive and Negative Affect Schedule (Watson & Clark, 1999), including the negative and positive affect scales (10 items each) and additional items from the joviality, guilt, serenity and sadness subscales. Additional items specific to this study (apathetic, numb) will also be included. Participants will rate how often they generally feel each emotion on a 0 (very slightly or not at all) to 4 (extremely) Likert scale. This questionnaire will also be administered through an online link for a follow-up assessment the academic quarter after the participant completes her session.

3.2 Vulnerability factors that may moderate effects of stress on reward.

3.2a *Consummatory anhedonia.* The Snaith Hamilton Pleasure Scale (Snaith et al., 1995) assesses the ability to experience pleasure in the last few days on a scale of 1(strongly disagree to 4 (strongly agree). Participants respond to statements such as "I would find pleasure in small things, e.g. bright sunny day, a telephone call from a friend."

3.2b *Social anhedonia*. The Chapman Social Anhedonia Scale Revised (CSASR; Mishlove & Chapman, 1985) is one of the most widely used measures of anhedonia and consists of 40 yes/no questions. It assesses pleasure experienced when interacting with others and interest in having close social connections (e.g., "A car ride is much more enjoyable if someone is with me.") Higher scores indicate less ability to experience pleasure. The Multidimensional Personality Questionnaire-Brief Form – Social Closeness Scale (Patrick, Curtin, & Tellegen, 2002) consists of 12 yes/no items. It will be used because the CSASR has been criticized for poor psychometric functioning (Olino et al., 2016) and cultural bias (Leventhal et al., 2006) and researchers have advocated its use for assessment of social anhedonia (Olino et al., 2016; Reise, Horan, & Blanchard, 2011). To control for potential confounding of social anhedonia with social phobia, the 3-item Mini-Social Phobia Inventory (MSPI; Connor, Kobak, Churchill, Katzelnick, & Davidson, 2001), will also be administered. The MSPI has shown sound psychometric properties, including strong sensitivity in treatment seeking samples (Weeks, Spokas, & Heimberg, 2006). To control for potential confounding of social anhedonia with lack of social support, will also examine perceptions of social support through the attachment subscale of the Social Provisions scale (Cutrona & Russel, 1987; 4 items).

3.2c *Physical anticipatory and physical consummatory anhedonia.* The Temporal Experience of Pleasure Scale (Gard, Gard, Kring, & John, 2006) is an 18 item scale that assesses anticipatory and consummatory anhedonia in the physical realm. Participants rate how true each statement is for them in general on a 1 (very false for me)

to 6 (very true for me) scale. Example items: "I really enjoy the feeling of a good yawn" and "When ordering something off the menu, I imagine how good it will taste."

3.2d *Reward Sensitivity.* Behavioral inhibition and behavioral activation scales (BIS/ BAS; Carver & White, 1994). These scales are proposed to represent two basic motivational systems, an approach oriented appetitive system and an avoidance oriented inhibited system. This 24 item scale assesses individual differences in the sensitivity of each system. The BAS is composed of the following three subscales: drive, fun seeking, and reward responsiveness. Participants rate their agreement with statements like "I often act on the spur of the moment" on a 1 (very true for me) to 4 (very false for me) scale.

3.2e *State anhedonia.* The Mood and Anxiety Symptom Questionnaire anhedonia subscale (Watson et al., 1995) is 14 items and assesses anhedonic symptoms over the past week. Participants indicate how often they have had "feelings, sensations, problems and experiences that people sometimes have" such as "Felt like I had a lot of interesting things to do" on a 5-point Likert scale (1 = *not at all*; 5 = *extremely*). This questionnaire will also be administered through an online link for a follow-up assessment the academic quarter after the participant completes her session.

3.2f *Early life stress.* In the Risky Families Questionnaire (Repetti, Taylor, & Seeman, 2002), participants indicate the extent to which they lived in a home characterized by high conflict, low parental warmth, and a chaotic or unpredictable daily experience as a child. Items are rated on a 1 (*not at all*) to 5 (*very often*) scale. The Adverse Childhood Experiences checklist (ACEs) (Chapman et al., 2004; Dube, Felitti, Dong, Giles, & Anda, 2003) is a 10-item checklist including: parent separation/divorce, domestic violence, family member in prison, maltreatment, and family member with mental illness or substance abuse. This scale has been used extensively in both psychology, psychiatry, pediatric, and epidemiological research, where exposure to more than 3 ACEs is associated with increased risk for both physical and mental illness (Chapman et al., 2004; Chapman, Dube, & Anda, 2007; Dube et al., 2003).

3.2g *Depressive symptoms.* The 20-item *Center for Epidemiologic Studies-Depression* scale (Radloff, 1977) is a reliable and valid 20-item self-report scale developed for the general population to assess depressive symptomatology. Participants are asked to rate how often they have experienced depressed feelings, attitudes, and behavioral symptoms during the past week (0 = *rarely*; 3 = *most of the time*). This questionnaire will also be administered through an online link for a follow-up assessment the academic quarter after the participant completes her session.

3.2h. *Perceived stress* will be assessed with the 10-item *Perceived Stress Scale* (PSS) (Cohen, Kamarck, Mermelstein, 1983), a widely used scale assessing how often events had been experienced as unpredictable, uncontrollable, and overwhelming over the past week (0 = never; 4 = very often). Individuals with higher perceived stress exhibit blunted reward-learning (Pizzagalli et al., 2007).

3.2i *Emotion Regulation.* The 5 item self-kindness subscale from the Self-Compassion scale (Neff, 2003) and the 6 item rumination subscale from the Rumination and Reflection scale (Trapnell & Campbel, 1999) will be administered to assess levels of positive and negative emotion regulation. This will allow us to examine the extent to which basic reward processing is associated with regulation of emotion.

3.2j. *Positive Psychological Constructs.* The Ego Resiliency Scale (Block & Kremen, 1996; 14 items) will be used to assess trait resilience, and the Mental Health Continuum Short Form (Keyes, 2002; 14 items) will be used to assess eudaimonic and hedonic well-being. The Mindful Attention Awareness Scale (MAAS) will be used to assess trait mindfulness (Brown & Ryan, 2003; 15 items). These measures will allow us to examine the extent to which reward processing is associated with different dimensions of psychological well-being.

4. Compensation

Participants will receive course credit through SONA for their participation. Participants will be told they can also win the summed amount of two randomly selected trials from one of the behavioral reward tasks (the EEfRT) and their winnings from a second reward task (the PRT). Participants will only receive this money if they complete a brief online questionnaire assessing depressive symptoms, mood and state affect the subsequent academic quarter. Thus, participants will not receive monetary reimbursement while they are participating under the SONA system in the current academic quarter. Partial payment will not be offered.

5. Potential Benefits of the Proposed Research to Participants

There are no direct benefits.

6. Importance of the Knowledge to be Gained

This project will advance our understanding of the effects of stress and inflammation on anhedonia, an important psychological construct that is both a symptom of depression and a potential mechanism leading to increased risk for development of depression. Understanding factors that give rise to anhedonia will ultimately contribute to more specialized treatment that is targeted at specific symptoms of depression.

7. Protection of Human Subjects

7.1. Known or Expected Risk for Participants and Procedures to Minimize Risk

7.1a. *Risk to confidentiality and privacy.* RARE. As in any project involving multiple sources of data, there are potential risks to confidentiality. For example, there is a potential risk to confidentiality if unauthorized individuals access subjects' records. There may be inadvertent risks to confidentiality if questionnaires or interviews are misplaced or lost. In order to minimize risks to confidentiality and privacy several measures will be taken. All research personnel are required to take the CITI Ethics in Research with Human Subject certification as well as take the utmost precautions in protecting health information. All subjects are assigned a Research ID number, which will be the only identifier assigned to all research data. All collected materials will only contain this number as an identifier and will be stored in locked file cabinets or a secure freezer in the UCLA Health Psychology Laboratory. Only the PI and authorized study personnel will have access to the Research ID number. Electronic copies of research results will be stored in password protected computers and in a backup server only accessible to the primary investigator. To protect privacy during the laboratory session, the PI and/or authorized study personnel will meet all participants at the Mind-Body Laboratory at UCLA, and obtain informed consent in a private room. This private room will also be used to complete computer tasks and questionnaires. Visit 2 will occur in a private room at the CTRC.

7.1b. *Risks related to laboratory tasks.* COMMON. It is possible that removal of blood may be associated with slight pain from the needle prick and/or that a bruise may develop at the site of the needle puncture. In rare cases, fainting or infection may occur. All blood draws will be done using sterile procedures by a registered nurse to minimize these risks. There are no known risks associated with the collection of saliva. For people who tend to have a dry mouth and produce little saliva, there can be some discomfort in chewing on the cotton cloth. It is also possible that some participants will experience some emotional discomfort during some of the cognitive tasks as these include the presentation of emotional stimuli (e.g., sad faces). In order to minimize risks related to laboratory tasks several measures will be taken. The participants will be accompanied by a trained and experienced research assistant during all laboratory tasks. These research staff will have experience working with research participants and will be trained to monitor whether the participant displays a level of discomfort

that is beyond what is expected during these tasks. All research procedures will be terminated if a participant displays such level of discomfort.

7.1c. *Risks related to mental health concerns*. INFREQUENT. Participants may experience discomfort when completing psychological questionnaires, including items pertaining to depression and anxiety. In order to minimize risks related to mental health concerns, all participants will be provided with information regarding access to mental health services.

8. Data and Safety Monitoring Plan

8.1 Data Monitoring Plan

The PI or authorized study personnel will assign a Research ID number to each participant at the time of study entry. Only the PI and authorized study personnel will have access to a locked, password-protected document linking identifiable information to the Research ID number.

All data collected will include the ID number and no identifying information. Online questionnaire data will be collected using the online survey platform Qualtrics. Qualtrics uses Transport Layer Security (TLS) encryption. Participants will be sent a personalized link that already contains their study ID number and will not be asked to enter personally identifiable information. This way, the online survey information will be kept separate from any personally identifying information. Electronic data will be stored on a secure server in the Department of Psychology; only the PI and authorized personnel will have access to this data. Data will be reported as averages and no individual participant's data will be identifiable.

Biological samples will be labeled only by code number and will be stored in a -20° C freezer in a locked room within the PRP at the CTRC or at the UCLA Health Psychology Laboratory until assayed. Per UCLA Clinical Laboratory procedure for research studies, blood samples will not be identified by medical record numbers (Anonymous ID), and will not be entered into the PCMIS/MCCS system.

Upon completion of data collection, the principal investigator will retain de-identified original paper data in a locked file cabinet, and all electronic data will be stored on a secure server operated by the College of Life Sciences and backup media in the Department of Psychology. A separate, password protected file linking each participant's unique PID to any identifying data will be kept by Principal Investigator in an encrypted computer.

8.2 Risk Management Procedures

8.2a Referral for participant depression and other psychopathology. As part of the study, depression or distress in the participant may become evident during the study. Research staff will be trained to recognize signs of distress during the stress protocol that are beyond a normative response. If a participant evidences distress during the TSST, research assistants will be trained to stop the procedure and ask the participant if she desires to continue. If the participant does not wish to continue, research assistants will have a prepared debriefing script that explains that the speech task and math task were designed to elicit stress and do not actually reflect on the participant's performance. They will also explain that the participant was not actually being evaluated at any point in time. Participants will be provided resources to obtain mental health services at the UCLA campus clinic, and receive the number of a 24-hour Crisis Hotline.

8.2b Adverse event (AE) reporting. All serious and unexpected adverse events will be reported to the IRB within 24 hours the awareness of their occurrence. All other adverse events will be reported to the IRB in aggregate with annual reports. We will monitor participants frequently as to clinical response, to reduce the likelihood of adverse events.

9. Statistical Approach

9.1 Sample Size Estimation

Specifying an α value of .05, a sample size of 57 is required to provide 80% power to detect a significant indirect effect in the mediation model. Sample size estimates come from Monte Carlo power analysis using the software developed by Schoemann and colleagues (2017). Estimates for standard deviations and correlations among the predictor, mediator and outcome variable come from pilot data in our lab (unpublished) as well as our prior work on peripheral IL-6 and PRT performance. We assumed a moderate correlation ($r = .5$) between our predictor (TSST vs. P-TSST) and mediator (change in IL-6).

9.2 Statistical Analyses Overview

Single mediation analyses will be conducted to evaluate the hypothesis that IL-6 mediates effects of stress on change in performance on the EEfRT and PRT. The predictor is group assignment (TSST/P-TSST). The mediator variable is an IL-6 change score (IL-6 at 120 minutes minus IL-6 at baseline) with higher values indicating a greater increase in IL-6. The outcome variables are also change scores (post-TSST/P-TSST performance minus baseline performance). The mediation model provides coefficients that test the extent to which group assignment predicts change in IL-6 (i.e., did the stress group have a greater inflammatory response than the control group) and the extent to which changes in IL-6 predict changes in reward task performance (controlling for group assignment). The significance of the mediated effect (i.e., testing whether IL-6 mediated the effect of condition on reward task performance) is tested using a non-parametric bootstrap approach implemented using the *paramed* module in STATA 13.1. Using 10,000 bootstrap samples for each analysis, point estimates, standard errors and bias-corrected bootstrap confidence intervals will be obtained for the mediated effect; the mediated effect is significant if the confidence intervals do not include zero.

9.3 Hypothesis Testing

Hypothesis 1 proposes that increases in inflammation will statistically mediate the effect of condition (TSST versus P-TSST) on reward processing deficits. Mediation analyses will be conducted using the paramed module in STATA, which allows for the inclusion of covariates and provides non-parametric bootstrapped confidence intervals to test the significance of the indirect effect. Separate analyses for each of the three dependent variables (e.g., response bias, attentional bias scores, proportions of hard versus easy trials) will be conducted.

1a. Probabilistic reward task. The reward learning task (PRT) will be administered before and after the TSST/P-TSST. At each assessment a response bias score will be computed as an index of reward responsiveness. Change in response bias is calculated by subtracting the total response bias at pre-TSST/P-TSST from the total response bias at post-TSST/P-TSST. This change score is the outcome variable for the mediation analysis.

1b. Effort Expenditure for Rewards Task - motivation. The proportion of high effort trials chosen is calculated for the baseline assessment and for the post-TSST assessment. A change score is then calculated by subtracting the proportions chosen at Visit 1 from proportions chosen post-TSST/P-TSST; this change score is the outcome variable for the mediation model. Consistent with prior studies, change scores at each of three levels of probability are also calculated.

1c. Effort Expenditure for Rewards Task - sensitivity. Generalized estimating equations (GEEs) with a binary logistic model and exchangeable working correlation structure will be conducted within the stress group. 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. The

predictor of interest is a 2-way interaction term between reward magnitude and change in IL-6; this term assesses whether increases in reward magnitude predict increased choice of high effort trials less robustly in the context of greater increases in IL-6.

1d. Dot probe task. An attentional bias score will be created by subtracting response time to neutral faces from response time to happy faces. Change in attentional bias is calculated by subtracting the total attentional bias score at pre-TSST/P-TSST from the total attentional bias score at post-TSST/P-TSST. This change score is the outcome variable for the mediation analysis.

1e. Face morphing task. A change score for reaction time latency for detection of positive faces will be created by subtracting response time to positive faces at pre-TSST/P-TSST from reaction time at post-TSST/P-TSST. This change score is the outcome variable for the mediation analysis.

Hypothesis 2 proposes that vulnerability factors will moderate the association between the stress-induced inflammatory response and alterations in reward processing. Moderated mediation models for each of the three vulnerability factors (history of early adversity, trait anhedonia, current depressive symptoms) will be conducted using the Hayes Process Module in SPSS.

Hypothesis 3 proposes that compared to those in the P-TSST, stressed participants will report increased negative and reduced positive affect immediately post stressor. Multiple regression analysis will be used to test for group differences in affect following the TSST/P-TSST; baseline affect will be included as a covariate and group assignment (TSST/P-TSST) is the predictor of interest. Changes in positive affect are hypothesized to correlate with changes in reward task performance; this will be assessed with bivariate correlations between change scores within the stress group.

Hypothesis 4 proposes that the degree of reward dysregulation in response to stress-induced inflammation will predict increases in depressive symptoms and perceived stress, and decreases in positive affect, four months following the experimental session. Multiple regression analyses will be conducted for participants who underwent stress, with change in the psychosocial measure as the outcome (study entry to 4-month follow up), and change in reward processing (pre to post-TSST) as the predictor.

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