Brain, Behavior, and Immunity 94 (2021) 60–70

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Goal-striving tendencies moderate the relationship between reward-related brain function and peripheral inflammation

Iris Ka-Yi Chat [a], Robin Nusslock [b,c], Daniel P. Moriarity [a], Corinne P. Bart [a], Naoise Mac Giollabhui [a], Katherine S.F. Damme [b,d], Ann L. Carroll [b], Gregory E. Miller [b,c], Lauren B. Alloy [a,*]

[a] Department of Psychology, Temple University, Philadelphia, PA, USA
[b] Department of Psychology, Northwestern University, Evanston, IL, USA
[c] Institute for Policy Research, Northwestern University, Evanston, IL, USA
[d] Institute for Innovations in Developmental Sciences (DevSci), Northwestern University, Evanston and Chicago, IL, USA

ARTICLE INFO

Keywords:
Cytokines
fMRI
Goal-striving
Inflammation
Neuroimmune
Reward anticipation
Orbitofrontal cortex
Nucleus accumbens

ABSTRACT

Inflammation is associated with both lower and higher activity in brain regions that process rewarding stimuli. How can both low and high sensitivity to rewards be associated with higher inflammation? We propose that one potential mechanism underlying these apparently conflicting findings pertains to how people pursue goals in their environment. This prediction is based on evidence that both an inability to disengage from unattainable goals and low interest in and pursuit of important life goals are associated with poor health outcomes, including inflammation. Accordingly, this study examined the relationship between reward-related brain function and peripheral inflammation among individuals with different levels of ambitious goal-striving tendencies. Eighty-three participants completed an ambitious goal-striving tendency measure, an fMRI Monetary Incentive Delay task assessing orbitofrontal cortex (OFC) and nucleus accumbens (NAc) activation during reward anticipation and outcome, and a venous blood draw to assess the inflammatory biomarkers interleukin (IL)-6, IL-8, tumor necrosis factor-alpha, and C-reactive protein, from which we computed an inflammation composite score. We observed a reward anticipation by goal-striving interaction on inflammation, such that high OFC and NAc activation to reward anticipation (but not outcome) were associated with more inflammation, among high goal-striving individuals. By contrast, low NAc activation during reward anticipation (but not outcome) was associated with more inflammation, among low goal-striving individuals. The current study provides further evidence that both *blunted* and *elevated* reward function can be associated with inflammation. It also highlights the role that goal-striving tendencies may play in moderating the relationship between neural reward anticipation and inflammation.

1. Introduction

Accumulating evidence highlights the importance of bidirectional signaling between the brain and the immune system in emotion, motivation, and multiple mental and physical health problems (Felger et al., 2016; Haroon et al., 2012; Nusslock and Miller, 2016). Much of this research has focused on brain systems that are involved in processing rewards and facilitating goal-directed behaviors, including the ventral striatum (VS)/nucleus accumbens (NAc) and the orbitofrontal cortex (OFC). Animal and human research suggests that peripheral inflammatory mediators (e.g., cytokines) can access the brain where they alter sensitivity to rewarding stimuli in the VS and the OFC (Miller, et al., 2013; Weber et al., 2017). Research also shows that reward signaling in the brain can modulate inflammation in the periphery (Schiller et al., 2021). Much of the research on reward-immune signaling has focused on depression, and finds that blunted sensitivity to rewards is associated with heightened inflammation (Capuron et al., 2012; Felger et al., 2016; Mac Giollabhui et al., 2020; Miller et al., 2009). However, elevated reward-related brain activity and behavior also can initiate inflammatory signaling (Ben-Shaanan et al., 2016), and individuals with bipolar disorder, which is associated with high levels or reward sensitivity, display heightened inflammation (Alloy et al., 2012; Modabbernia et al.,

* Corresponding author.
E-mail address: lalloy@temple.edu (L.B. Alloy).

https://doi.org/10.1016/j.bbi.2021.03.006
Received 18 September 2020; Received in revised form 4 March 2021; Accepted 5 March 2021
Available online 9 March 2021

2013). How can both low and high sensitivity to rewards be associated with elevated inflammation? We propose that the propensity to set highly ambitious goals for oneself, one's ambitious goal-striving tendencies, may help us answer this question. Accordingly, the present fMRI study examines whether ambitious goal-striving tendencies moderate the relationship between reward-related brain activation and peripheral inflammation.

Reward processing is linked to a corticostriatal neural circuit that involves the OFC and NAc, among other regions (Haber and Knutson, 2010). The OFC is involved in assigning value to both social and achievement-oriented rewards and assessing the probability of reward receipt. The NAc is a subnuclei of the ventral striatum that is involved in the hedonic evaluation of social and achievement-related rewards, especially anticipation and detection of rewards (Dillon et al., 2008; Haber and Knutson, 2010). Disrupted signaling in the OFC and NAc are associated with impulsivity and mental and physical health problems, including substance use and mood disorder symptoms (McCabe et al., 2012; McMurray et al., 2016; Nusslock et al., 2012; Nusslock and Miller, 2016; Pizzagalli, 2014; Rolls et al., 2020).

Reward processing in the corticostriatal circuit is centrally involved in bidirectional signaling between the brain and the immune system. Inflammatory signals in the periphery (e.g., cytokines) can spread to the brain through multiple mechanisms, including active transport, engaging vagal fibers, or entering at circumventricular organs or leaky regions of the blood–brain barrier (Irwin and Cole, 2011; Weber et al., 2017). Once in the brain, inflammatory molecules have been shown to lower reward signaling in the corticostriatal circuity (Irwin and Cole, 2011; Weber et al., 2017; Capuron et al., 2012; Felger et al., 2016; Haroon et al., 2016; Miller et al., 2013), potentially through blunting dopamine transmission in the NAc (Capuron et al., 2012; Miller et al., 2013). This signaling is a two-way street, and reward circuitry in the brain also can modulate inflammation in the periphery directly via the sympathetic nervous system (Ben-Shaanan et al., 2016; Schiller et al., 2021), or indirectly through reward-related behaviors (Nusslock and Miller, 2016). This signaling is highly adaptive when regulated, as it modulates metabolic resources for fighting pathogens and wound healing. When dysregulated or chronic, however, inflammation can result in sustained alterations in reward responsivity and risk for mental and physical health problems, particularly depression (Lacourt et al., 2018a, 2018b; Dantzer et al., 2008).

Intriguingly, a growing number of studies suggest that the relationship between reward function and inflammation in the periphery is context-dependent. For example, Lasselin et al. (2017) showed that individuals with heightened inflammation from exposure to an endotoxin were more willing to exert effort when the probability of obtaining a reward was high. Much of this work manipulated inflammatory signaling and examined its effect on reward-related brain function (Eisenberger et al., 2010, 2017; Inagaki et al., 2015; Irwin et al., 2016; Felger et al., 2016; Harrison et al., 2016; Lasselin et al., 2017; Muscatell et al., 2016). Although there are fewer studies that have examined the influence of reward-related brain function on inflammation, indirect evidence suggests that both elevated and blunted reward function may be associated with heightened inflammation. For example, individuals with bipolar spectrum disorders, which are characterized by a heightened sensitivity to rewards and increased reward-related brain function (Alloy et al., 2016; Nusslock and Alloy, 2017), typically display high levels of inflammatory biomarkers, and meta-analyses document elevated pro-inflammatory cytokines in both manic and bipolar depressive states (Modabbernia et al., 2013; Munkholm et al., 2013). By contrast, individuals with unipolar depression, which is characterized by a blunted sensitivity to rewards and decreased reward-related brain function, also typically display high levels of inflammation (Capuron et al., 2012; Felger et al., 2016; Mac Giollabhui et al., 2020; Miller et al., 2009). Thus, the question that drives this paper is how can both low and high sensitivity to rewards be associated with elevated inflammation? Some have argued that, in a high-stress environment, individuals with both high and low reward responsivity are prone towards engaging in high-risk, unhealthy behaviors that increase inflammation (e.g., high-fat diet, substance use; Alloy et al., 2009; Blum et al., 2014; Büchel et al., 2017; Gearhardt et al., 2011; O'Connor et al., 2009; Volkow et al., 2012). Here we consider another possibility and examine the tendency to set highly ambitious goals for oneself as a trait-like characteristic that may reflect a high-stress context and moderate levels of inflammation among individuals with high and low reward responsivity. In other words, although this study did not directly test the role of stress, the tendency to set highly ambitious goals may be important as a contextual factor.

Ambitious goal-striving tendencies refer to the inclination of setting highly ambitious goals and working towards them. If regulated (e.g., a realistic goal is set), goal-striving is highly adaptive and maximizes the likelihood that such goals will be reached, promoting well-being and good health. However, if dysregulated (e.g., an overly ambitious goal is set), excessive goal-striving can be maladaptive. For individuals with high responsiveness to potential rewards and motivation to approach them, a concurrent tendency to set highly ambitious, unrealistic goals may induce high levels of negative mood (e.g., anger, dysphoria) by constantly putting them in a position of attempting to pursue those impossible goals. Indeed, giving up on pursuing a goal may be the more adaptive response when the goal is impossible to reach, because it allows individuals to avoid repeated distress from multiple obstacles and failures, and any mental and physical health consequences that ensue. For example, Miller and Wrosch (2007) reported that individuals who self-reported having a difficult time disengaging from unattainable goals displayed increasing levels of the inflammatory molecule C-reactive protein over 12 months. This finding suggests that, in some contexts, persistence may compromise well-being and health, given that excessive and persistent inflammation can generate risk for numerous mental and physical illnesses (Kaptoge et al., 2014; Osimo et al., 2019). In line with this view, individuals who report difficulty in disengaging from unreachable goals report worse self-reported health, worse subjective well-being, and altered cortisol output relative to people who report more easily giving up unattainable goals (Miller and Wrosch, 2007; Wrosch et al., 2003, 2007, 2013).

The question of whether and how ambitious goal-striving tendencies can modulate the relationship between low reward responsiveness and inflammation is more complex, because a low tendency to set highly ambitious goals can represent either realistic goal-setting or lack of aspiration, therefore complicating the interpretation. However, it is possible that a tendency to set highly ambitious goals buffers individuals with low reward responsivity from learned helplessness (i.e., quickly believing that one is incapable of accomplishing a goal), negative mood states (e.g., dysphoria, anhedonia), and unhealthy behaviors that promote inflammation. Thus, individuals with high reward responsiveness may be susceptible to health consequences if they exhibit ambitious goal-striving tendencies, whereas such ambitious goal-striving tendencies may serve as a protective factor for those with low reward responsiveness. However, to our knowledge, there is a gap in the literature examining the role of goal regulation in the association between reward function and inflammation.

We predict that ambitious goal-striving tendencies will moderate the relationship between reward-related brain function and inflammation. To our knowledge, no studies have elucidated the relationship between ambitious goal-striving tendencies and reward-related brain function. However, as a broad personality characteristic, ambitious goal-striving tendencies likely involve multiple different psychological and neural processes. By contrast, reward anticipation specifically involves hedonic responses to reward stimuli. This conceptualization suggests that ambitious goal-striving tendencies and reward anticipation are two unrelated constructs, which implies that goal-striving tendencies may not mediate reward anticipation's association with inflammation. Instead, the stable and trait-like nature of ambitious goal-striving tendencies suggests this construct is more appropriate as a moderator of the

relationship between reward-brain function and inflammation. In particular, we predict that individuals with high levels of reward responsivity in the NAc and OFC, who also report highly ambitious goal-striving tendencies, will display higher levels of peripheral inflammatory biomarkers. By contrast, we predict that individuals with lower levels of reward responsivity in the NAc and OFC and less ambitious goal-striving tendencies also will show higher inflammation. Furthermore, we predict these relationships will be specific to neural responses to anticipation, but not receipt, of monetary reward, given emerging evidence that the "wanting" (instead of "liking") aspect of reward function commonly is linked to inflammation (Eisenberger et al., 2010; Felger and Treadway, 2017) and behaviors that promote inflammation (Argyropoulos and Nutt, 2013; Dillon et al., 2014; Nusslock and Miller, 2016; Sherdell et al., 2012; Volkow et al., 2012). Our objective also was to assess whether ambitious goal-striving tendencies uniquely moderate the relationship between reward-related neural activity and inflammation after adjusting for loss-related neural activity, given a possible link between anticipatory response to losses and inflammation (Harrison et al., 2016; Nusslock and Miller, 2016). To test these predictions, young adult participants completed a goal-striving questionnaire and the monetary incentive delay task (MID) during fMRI scanning to assess reward-related brain function (i.e., activation to reward anticipation vs. outcome). We also measured circulating inflammatory biomarkers [interleukin (IL)-6, IL-8, tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP)], and these measures were averaged to form a composite. The results from these analyses will inform our understanding of the contextual and psychological factors that modulate neuroimmune signaling.

2. Material and methods

2.1. Participants

Participants were drawn from the Teen Emotion and Motivation (TEAM) Project (Alloy et al., 2012), a large longitudinal study examining the relationship between reward responsivity, motivation, and risk for mood disorders. Exclusion criteria for Project TEAM included a history of psychosis. At the time of recruitment into Project TEAM, participants (ages 14–19) were classified as having moderate levels of reward responsivity or high levels of reward responsivity based on both the Behavioral Inhibition System (BIS)/Behavioral Activation System (BAS) Scale (Carver and White, 1994) and the Sensitivity to Punishment (SP)/Sensitivity to Reward (SR) Questionnaire (Torrubia et al., 2001). This recruitment approach was relevant to the overall aims of Project TEAM (Alloy et al., 2012). An advantage of this recruitment method for the present analyses is that it increased the likelihood of some participants exhibiting extreme neural reward responsivity on the MID task. Further details regarding screening and eligibility criteria have been described elsewhere (Alloy et al., 2012).

A total of 133 participants from the larger project completed a single MRI session approximately 24 months (SD = 27 months) after the start of Project TEAM. We excluded participants from the MRI session based on the following criteria: ferrous metal in any part of the body, lifetime history of head trauma, claustrophobia, left-handedness, and pregnancy. Twenty-six participants were excluded due to excessive head motion (>3mm), and four other participants were excluded due to task acquisition errors. Twenty participants were excluded because they did not provide a blood sample for inflammation analyses (n = 19) or were missing part of their goal-striving tendency questionnaire data (n = 1). Thus, the final analytic sample for the present study included 83 participants (54.22% female; 63.86% White, 22.89% Black, 9.64% Asian, 3.61% bi-/multiracial; M_{age} at blood draw = 21.06, SD_{age} = 2.18 years). This final analytic sample did not differ from participants excluded from the present study on gender ($\chi^2[1] = 0.689$, $p = .406$), race ($\chi^2[6] = 3.589$, $p = .732$), age at scan ($t[131] = -.175$, $p = .862$), trait reward sensitivity ($t[131] = 0.054$, $p = .957$), and mood disorder history ($\chi^2[1] = 0.077$, $p = .782$). Participants provided informed written consent and the Institutional Review Board at Temple University approved all study protocols.

2.2. Procedure

Participants completed the Willingly Approached Set of Statistically Unlikely Pursuits (WASSUP) scale to assess ambitious goal-striving tendencies at the beginning of their involvement in Project TEAM. A subset of Project TEAM participants completed the fMRI Monetary Incentive Delay (MID) task to assess reward-related brain function and a blood draw to assess circulating inflammatory biomarkers

2.3. Assessment of ambitious goal-striving tendencies

The WASSUP (Johnson and Carver, 2006) is a self-report questionnaire using a 5-point Likert scale (i.e., 1 = *no chance I will set this goal for myself* to 5 = *definitely will set this goal for myself*) to assess the likelihood of setting 30 highly ambitious and unrealistic goals (e.g., running a Fortune 500 company). A high score indicates a high tendency to set highly ambitious goals for oneself. A low score indicates a low tendency to set highly ambitious goals. The interpretation of low scores needs to be done cautiously because a low tendency does not necessarily represent a maladaptive goal regulation style (e.g., low aspiration), but could be realistic goal-striving. The WASSUP includes seven subscales: Popular Fame, Financial Success, Political Influence, idealized relations with Friends, idealized relations with Family, impact on World Well-being, and Fulfillment. We focused on the total scale score, given we did not have hypotheses about specific subscales and to minimize multiple comparisons. As noted, given that corticostriatal function has been associated with both achievement- and social-relevant reward (Nusslock and Alloy, 2017), we conducted exploratory analyses, in which we selected the achievement (combination of the WASSUP's Popular Fame and Financial Success subscales) vs. social (combination of the WASSUP's idealized relations with Friends and idealized relations with Family subscales) subscale to assess for domain specificity. The reliability for the WASSUP total scale in our data was α = 0.90, and the subscales ranged from α = 0.61-0.90. The present sample scored 2.82 on average (SD = 0.72), and the scores ranged from 1.433 to 4.533.

2.4. fMRI reward task

We used the Monetary Incentive Delay (MID) task (Samanez-Larkin et al., 2007) to assess reward-related brain function in the NAc and OFC (Fig. 1). First, a circle cue signaling a reward trial (the participant has the opportunity to Win $0.00, Win $1.50, or Win $5.00) or a square cue indicating a loss trial (the participant might Lose $0.00, Lose $1.50, or Lose $5.00) was displayed for 2 s. Then, a jittered fixation was presented followed by a solid white square. Participants were instructed to make a button response when the white square was still on the screen to either win money (reward trials) or avoid losing money (loss trials). On the Win Trials, participants won money if they pressed the white square in time and did not win money if they missed the target. On Loss trials, they avoided losing money if they pressed the white square in time and lost money if they missed the target. Feedback about the amount of money won or lost then was displayed for 2000 ms. Finally, a jittered fixation cross was presented for 2 s, 4 s, or 6 s as an intertrial interval. The initial target duration was calculated from each participant's mean hit reaction time on a MID practice run completed prior to the scan. The target duration was dynamically adapted during the task to maintain task difficulty so that participants accurately hit the target on 66% of trials, calculated separately for each trial type (i.e., Win $0.00, Win $1.50, Win $5.00, Lose $0.00, Lose $1.50, Lose $5.00). The six trial types each were presented 8 times in random order, totaling 96 trials, across two MID runs.

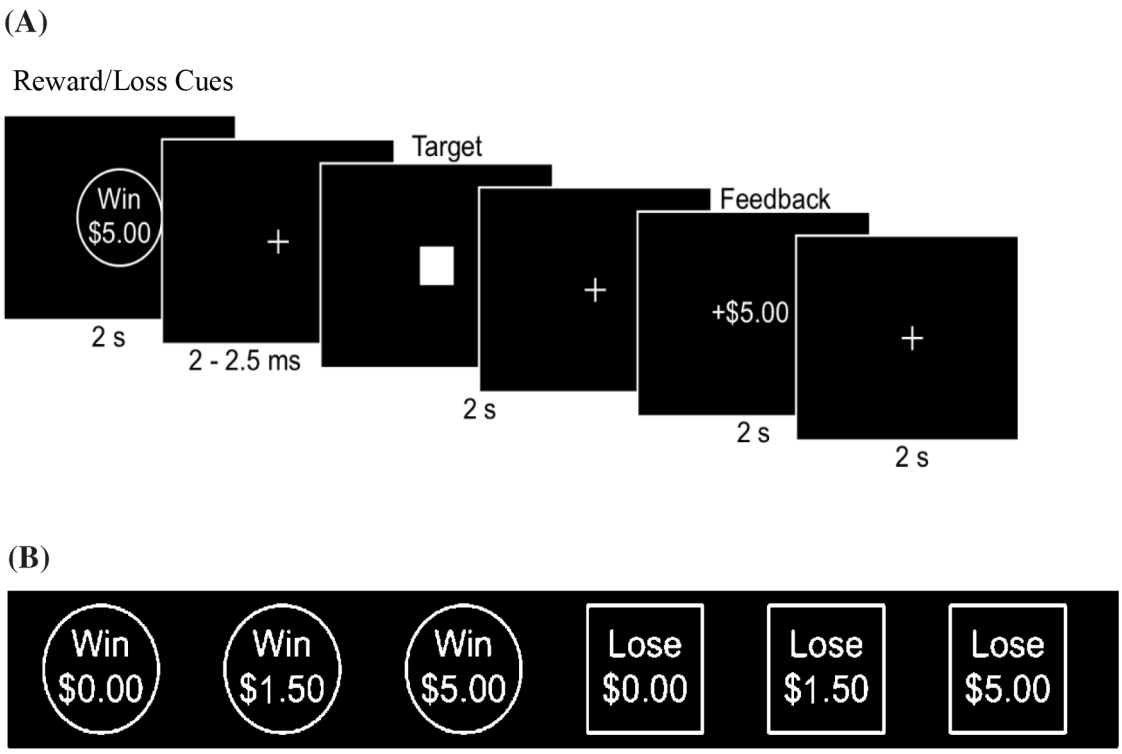

Fig. 1. The (A) trial structure and (B) possible reward and loss cues of the monetary incentive delay (MID) task used to examine reward and loss anticipation and outcome (adapted from: Young & Nusslock, Positive mood enhances reward-related neural activity, *Social Cognitive and Affective Neuroscience*, 2016, 11(6), 934–44, by permission of Oxford University Press).

2.5. fMRI data acquisition and analysis

Neuroimaging data were collected using a 3.0 Tesla Siemens Verio wide-bore MRI scanner with a standard 12-channel head coil at Temple University Medical Center. Structural 3D MPRAGE scans were collected in the sagittal plane using the following parameters: voxel size = .5x.5x1.0 mm, TR = 1600 ms, TE = 2.46 ms, FOV = 252, Flip Angle = 9°, 176 volumes. Functional BOLD scans were collected with the following parameters: coverage = 36 axial slices, 4 mm thick (FOV = 236 mm), matrix = 64x64, voxel size = 3.7x3.7x4.0 mm, TR = 2000, TE = 25 ms, Flip Angle = 70°, acquisition volumes = 292.

Data were analyzed using a general linear model carried out in SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). Functional images were realigned and corrected for errors in slice-timing. Images then were spatially normalized to MNI space and smoothed using a 6 mm full width at half maximum (FWHM) Gaussian kernel. Translational movement in millimeters (x, y, z) and rotational motion in degrees (pitch, roll, yaw) were calculated based on SPM8 parameters for motion correction of the functional images in each participant. The final sample had less than 3 mm of movement.

The hemodynamic signal was deconvolved using a general linear model identifying the six trial types during the MID anticipation and outcome phase. The anticipation phase was defined as the period after presentation of the cue indicating the possibility to win or lose money but prior to presentation of the target square (2–2.5 s). The outcome phase was defined as the period after presentation of the feedback (2 s). Six variables of no interest for motion were included. First-level voxel-wise *t*-statistics were computed for each participant contrasting reward (i.e., Win $1.50, Win $5.00) vs. non-reward (i.e., Win $0.00) trials to calculate reward anticipation and outcome, and loss (i.e., Lose $1.50, Lose $5.00) vs. non-loss (i.e., Lose $0.00) trials to calculate loss anticipation and outcome. We combined $1.50 and $5.00 trials to be consistent with previous research (e.g., Samanez-Larkin et al., 2007), for ease of interpretation, and to heighten reliability (i.e., more trials in the combined score). We conduct exploratory analyses with reward magnitude ($1.50 vs $5.00) as a factor.

We extracted parameter estimates (beta-weights) from predefined regions-of-interest (ROIs) for the NAc and OFC during reward and loss anticipation and outcome, and exported these parameter estimates into R and SPSS for analyses. We used an anatomically defined ROI for the bilateral OFC (Fig. 2A) and NAc (Fig. 3A) based on the Harvard Oxford Atlas. We used the Harvard Oxford OFC mask because it maximizes the balance between Type II and Type I error. For example, using multiple OFC ROIs to detect effects in smaller regions would increase risk of Type I error. On the other hand, using a mask that covers the entire OFC would require an especially large effect to observe significant associations, and thus, result in increased risk for Type II error. Although this mask excludes portions of the supramedial OFC, it does cover a relatively large portion of the OFC, while at the same time limiting risk for false negative findings. Finally, previous research examining the relationship between reward-related brain function and pro-inflammatory behaviors (e.g., addictive behaviors) frequently observe associations in more lateral regions of the OFC (Forbes et al., 2014; Nestor et al., 2018) . Thus, the OFC regions that the Harvard Oxford Atlas mask covers are particularly relevant to this area of research.

2.6. Inflammation biomarkers

We quantified plasma levels of CRP and cytokines IL-6, IL-8, and tumor necrosis factor-α to index inflammatory activity (Kaptoge et al., 2014; Nusslock and Miller, 2016; Osimo et al., 2019; Yuan et al., 2019). Antecubital blood samples were collected into an ethylenediaminetetraacetic acid-treated vacutainer and stored in a −80℃ freezer until the day of assay. Anthropometric and health measures (including height and weight to calculate body mass index [BMI], time of day of the blood draw, major illnesses, current use of prescription psychotropic and anti-inflammatory medications, current tobacco use, and time of last meal) were completed at the beginning of the blood draw. For feasibility

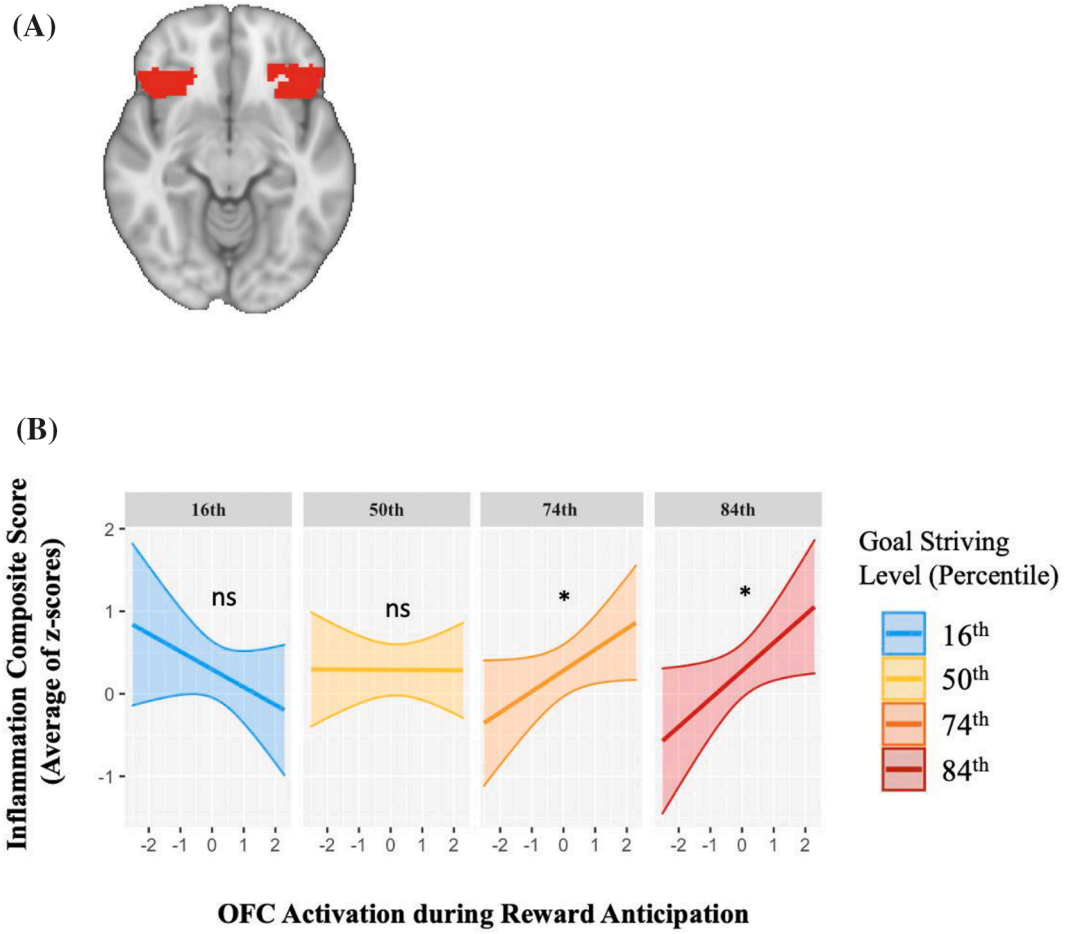

Fig. 2. (A) Structurally derived ROI for the bilateral orbitofrontal cortex (OFC) defined with Harvard Oxford Atlas template; ROI = Region-of-interest. (B) Inflammation composite score as a function of activation in the OFC during reward anticipation at the 16th, 50th, 74th, and 84th percentiles of self-reported goal-striving tendencies; ns = not significant; *$p < .05$.

purposes, we were not able to obtain a fasting blood draw or restrict the blood draw to a specific time of day, although most participants completed the blood draw in the afternoon. CRP was measured using a high-sensitivity immunoturbidimetric assay on a Roche/Hitachi cobas c502 analyzer, with average intra- and inter-assay coefficients of variations of 2.50% and 5.60%, respectively. The lower limit of detection for this assay is 0.20 mg/L. The cytokines were measured in duplicate by electrochemiluminescence on a SECTOR Imager 2400A using a Human Pro-Inflammatory Multiplex Ultra-Sensitive assay (MesoScale Discovery), according to the manufacturer instructions. The kit's lower limit of detection for these cytokines was 0.10 pg/mL. The average intra-assay coefficients of variations across runs were 3.79% (IL-6), 2.24% (IL-8), and 3.33% (TNF-α). Consistent with prior work from this dataset (Moriarity et al., 2020), we z-scored the natural log of the concentration value of each biomarker and then averaged them to form a composite score. A higher score on this composite reflects more inflammation. The use of a composite score benefits the analyses on inflammatory signaling. This approach lowers the chance of a Type I error by reducing the number of tests performed (in this case, by 75%). Further, it takes into account the dynamic activity among the inflammatory markers of interest acting on target cells and the cascading manner in which these markers are released.

2.7. Assessment of self-reported reward sensitivity and mood disorders

At initial screening, Project TEAM used the Behavioral Activation System (BAS) Total scale of the BIS/BAS questionnaire (Carver and White, 1994) and the Sensitivity to Reward (SR) scale of the SPSRQ Questionnaire (Torrubia et al., 2001) to assess self-reported reward sensitivity. Both the BAS total score ($\alpha = 0.80$) and the SR score ($\alpha = 0.76$) showed acceptable internal consistency in the screening sample, consistent with previous studies (Carver and White, 1994; Kelley et al., 2019; Meyer et al., 2001). We used the expanded Schedule for Affective Disorders and Schizophrenia-Lifetime (exp-SADS-L; Alloy et al., 2008; Endicott and Spitzer, 1978) interview to assess lifetime mood disorders, which we included as a covariate in all analyses in order to assess the relationship between reward-related brain function, goal-striving tendencies, and inflammation, above and beyond a history of mood disorders. Interrater reliability for mood disorder diagnoses on the exp-SADS-L in Project TEAM ranged from good to excellent based on 100 interviews (range $\kappa = 1.0$ to $\kappa = 0.88$).

2.8. Statistical analysis

Given previous literature showing that BMI (Bastard et al., 2006; Thomas and Apovian, 2017), current use of prescription psychotropic medication (O'Connor et al., 2009), a lifetime history of a mood disorder diagnosis (Rosenblat et al., 2014), current use of tobacco, current use of prescription anti-inflammatory medication (O'Connor et al., 2009), and gender (Moieni et al., 2019), are associated with inflammation, we controlled for these variables in all analyses. We also included the amount of time, measured in days, between the assessment of goal-striving tendencies and the blood draw, which for the large majority of participants occurred on the same day as the MRI scan, as a covariate

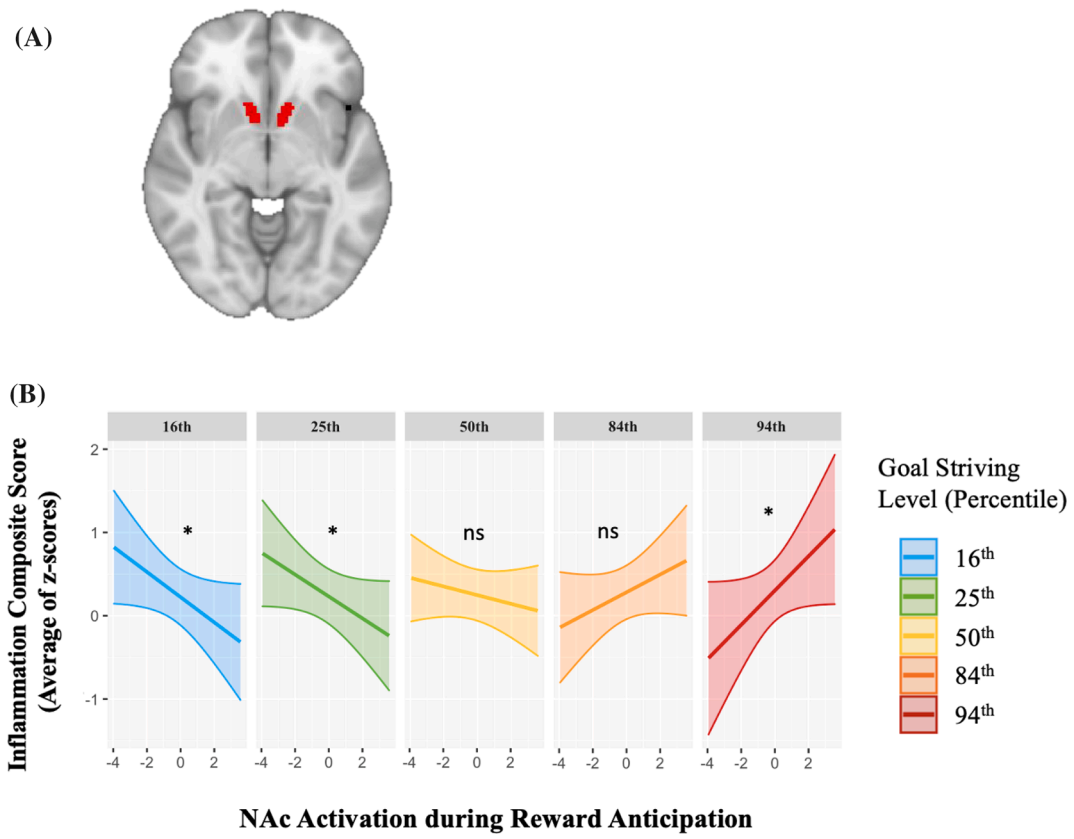

Fig. 3. (A) Structurally derived ROI for the bilateral nucleus accumbens (NAc) defined Harvard Oxford Atlas template; ROI = Region-of-interest. (B) Inflammation composite score as a function of activation in the NAc during reward anticipation at the 16th, 25th, 50th, 84th, and 94th percentiles of self-reported goal-striving tendencies; ns = not significant; * = $p < .05$.

in all analyses. Finally, we included the ROI beta-weight (for the NAc, OFC, respectively) for the corresponding loss contrast to examine the relationship between reward-related brain function, inflammation, and goal-striving tendencies above-and-beyond loss-related neural activity.

We conducted multiple regression analyses to test the hypothesis that goal-striving tendencies moderate the relationship between reward-related brain function and inflammation. We ran separate analyses for the NAc and OFC and for the anticipation and outcome period. Each of the analyses included the inflammation composite score as the dependent variable, BMI, gender, mood disorder history, current use of prescription psychotropic and anti-inflammatory medication, current use of tobacco, time between the WASSUP and blood draw, and either NAc or OFC activation to loss anticipation or outcome as covariates in the first block, ambitious goal-striving tendencies and NAc or OFC activation to reward anticipation or outcome in the second block, and the product term of the mean-centered goal-striving tendencies and either NAc or OFC activation to reward anticipation or outcome in the third block. For protection against type I error inflation due to multiple comparisons, we employed Fisher's protected *t*-test which requires a significant omnibus test in order to proceed to pairwise comparisons (Cohen et al., 2013). For any significant interaction results, the Johnson-Neyman technique was employed to probe the levels of the moderator (i.e., goal-striving tendencies) at the level of brain activation that was significantly associated with inflammation. We chose this technique over a traditional "simple slope" method (e.g., probing only the levels of the mean, and one standard deviation above and below the mean) because the Johnson-Neyman technique allows the report of the entire interval of the moderator, whereas the traditional "simple slope" method includes arbitrary fixed values of the moderator and yields results only for the cut-off values. Statistical analyses were conducted in R version 3.5.2 (R Core Team, 2018; Revelle, 2019; Tan, 2015; Hughes, 2020; Wickham and Miller, 2019) and IBM SPSS version 25, and figures were produced using the packages ggplots2 (Wickham, 2016) and graphics (R Core Team, 2018).

Follow-up analyses: 1) examined whether results were comparable if loss-related neural activity was excluded as a covariate 2); tested the primary hypotheses with loss-related neural activity (as opposed to reward-related neural activity) as the independent variable; 3) examined reward magnitude ($1.50 vs $5.00) as a factor, as opposed to combining reward $1.50 and $5.00 trials; and 4) assessed whether or not ambitious goal-striving tendencies for achievement (combination of the WASSUP's Popular Fame and Financial Success subscales) vs. social (combination of the WASSUP's idealized relations with Friends and idealized relations with Family subscales) goals had comparable effects on moderating the relationship between neural activation and inflammation. Details on these analyses are provided in the Supplementary Section.

3. Results

Demographic information for the current sample and data characterization are summarized in Table 1. There were no main effects for goal-striving tendencies (linear: $B = -0.847$, $SE = 0.653$, $t = -0.129$, $p = .201$, $\Delta R^2 = 0.015$; quadratic: $B = 0.148$, $SE = 0.110$, $t = 1.336$, $p = .186$, $\Delta R^2 = 0.016$), OFC reward anticipation (linear: $B = 0.400$, $SE = 0.117$, $t = 0.342$, $p = .733$, $\Delta R^2 = 0.001$; quadratic: $B = 0.060$, $SE = 0.066$, $t = 0.907$, $p = .368$, $\Delta R^2 = 0.008$), NAc reward anticipation (linear: $B = -0.069$, $SE = 0.105$, $t = -0.658$, $p = .513$, $\Delta R^2 = 0.004$; quadratic: $B = 0.018$, $SE = 0.025$, $t = 0.702$, $p = .485$, $\Delta R^2 = 0.005$), OFC reward outcome (linear: $B = 0.048$, $SE = 0.143$, $t = 0.338$, $p = .736$, $\Delta R^2 = 0.001$; quadratic: $B = -0.079$, $SE = 0.095$, $t = -0.826$, $p = .412$, $\Delta R^2 = 0.006$), or NAc reward outcome (linear: $B = 0.044$, $SE = 0.108$, t

Table 1
Summary of sample characteristics ($N = 83$).

Variable	*M (SD)*	*% (n)*
Gender		
Female		54.22 (45)
Race		
White		63.86 (53)
Black		22.89 (19)
Asian		9.64 (8)
Bi-/Multi-racial		3.61 (3)
Psychotropic medication status		
Not taken within past month		92.77 (77)
Currently taking		7.23 (6)
Body mass index	24.77 (5.70)	
Age (years)	21.06 (2.18)	
Goal striving tendencies	2.82 (0.71)	
Inflammatory Biomarkers		
C-reactive protein (mg/mL)	3.10 (0.50)	
IL-6 (pg/mL)	0.88 (0.86)	
IL-8 (pg/mL)	6.53 (2.11)	
TNF-α (pg/mL)	3.35 (0.87)	

Note. M, SD, % and n are used to represent mean, standard deviation, percentage, and frequency respectively. Abbreviations: IL, interleukin.

= 0.411, $p = .682$, $\Delta R^2 = 0.002$; quadratic: $B = 0.005$, $SE = 0.028$, $t = 0.173$, $p = .863$, $\Delta R^2 < 0.001$) on the inflammation composite score.

As predicted, there was a significant interaction between OFC activation during reward anticipation and goal-striving tendencies on the inflammation composite score, $B = 0.426$, $SE = 0.192$, $t = 2.216$, $p = .030$, $\Delta R^2 = 0.043$ (Fig. 2B). The Johnson-Neyman procedure showed that for participants in the top 25.66% of goal-striving tendency, elevated OFC activation during reward anticipation began to be associated with higher inflammation composite scores. We did not detect a significant interaction between OFC activation during reward outcome and goal-striving tendencies on the inflammation composite score, $B = -0.022$, $SE = 0.169$, $t = -0.128$, $p = .899$, $\Delta R^2 < 0.001$.

Also in line with prediction, there was a significant interaction between NAc activation during reward anticipation and goal-striving tendencies on the inflammation composite score, $B = 0.199$, $SE = 0.085$, $t = 2.337$, $p = .022$, $\Delta R^2 = 0.047$ (Fig. 3B). Like the OFC, Johnson-Neyman analysis showed that for participants in the top 5.87% of goal-striving tendency, elevated NAc reward activation began to be significantly associated with a higher inflammation composite score. We also found that for participants in the bottom 25.32% of goal-striving tendency, lower NAc reward activation began to be associated with higher inflammation composite scores. We did not detect a significant interaction between NAc activation during reward outcome and goal-striving tendencies on the inflammation composite score ($B = -0.029$, $SE = 0.070$, $t = -0.412$, $p = .682$, $\Delta R^2 = 0.002$)[1].

Exploratory analyses (a) indicated that results were comparable if loss-related neural activity in either the OFC or NAc were excluded as a covariate. (b) There were no significant interactions between loss-related neural activity in either the OFC or NAc, for either anticipation or outcome, with goal-striving tendencies on inflammation. (c) There was an interaction between NAc outcome to $1.50 and ambitious goal-striving tendencies, but significant results were not observed for other reward or loss magnitudes, suggesting that results from the present work were more robust for the combined Win ($1.50 and $5.00) reward metric. (d) Intriguingly, the only significant result for the effect of type of ambitious goal setting was an interaction between NAc reward anticipation and social-based goal-striving tendencies on inflammation. This suggests that tendencies to set ambitious social goals might be relevant for moderating the link between monetary reward-related brain function and inflammation. The results for these follow-up analyses are presented in the Supplementary Section.

4. Discussion

The present study reports, for the first time, that goal-striving tendencies moderate the relationship between reward-related brain function and inflammatory biomarkers. Specifically, we report that, among individuals with high goal-striving tendencies, heightened NAc and OFC activity during reward anticipation (but not reward outcome, loss anticipation, or loss outcome) was associated with heightened inflammation. These relationships were observed after adjusting for BMI, gender, time between assessments, current use of tobacco, prescription anti-inflammatory, and psychotropic medications. The results also were comparable with or without a lifetime history of a mood disorder as a covariate, suggesting that it was not purely a product of mood disorder history. The results held significant regardless of the inclusion of ROI activation during loss anticipation or outcome as a covariate, offering further support that our results were observed above and beyond loss-related neural activity.

Our findings are consistent with studies suggesting that a tendency to "press on" can be maladaptive and physically taxing when there are serious obstacles to realizing goals or the pursued goals are unrealistic or unattainable (Miller and Wrosch, 2007; Wrosch et al., 2013). For example, individuals reporting a hard time disengaging from unattainable pursuits display increasing inflammation over time, whereas people who are able to disengage from such goals enjoy better well-being, lower stress biology, and fewer symptoms of everyday illness (Barlow et al., 2020; Castonguay et al., 2014; Miller and Wrosch, 2007). The combination of ambitious goal-striving and high reward anticipation might lead people into high-stakes situations where substantial and persistent effort is needed to realize their aspirations. When goal achievement is possible, those efforts may pay off. However, when opportunities for success are not favorable, but the individual is highly motivated, the resulting mismatch may lead to increased inflammation, which is associated with numerous mental (Dantzer et al., 2008; Harrison et al., 2016; Hutchinson et al., 2011; Miller et al., 2009; Miller and Cole, 2012; Stewart et al., 2009) and physical health problems (Hotamisligil, 2006; Libby et al., 2009; Mantovani et al., 2008; Odegaard and Chawla, 2013; Ridker, 2007; Scrivo et al., 2011).

One possible mechanism through which this combination (high levels of reward anticipation and ambitious goal-striving) could trigger inflammation is negative mood states involving frustration, anger, and exhaustion (Hundt et al., 2013). These mood states, when chronic, may disrupt the autonomic nervous system and the hypothalamic–pituitaryadrenal axis, both of which are involved in regulating peripheral inflammatory signaling (Irwin and Cole, 2011; Miller et al., 2011; Nusslock and Miller, 2016; Pace and Miller, 2009; Raison and Miller, 2003; Rolls et al., 2020). A second possibility is that individuals with high levels of reward anticipation may be likely to ruminate on their failures to attain those goals, and they may ruminate even more if they also have tendencies to pursue highly ambitious goals, given more exposure to goal failures. The ruminative process, in turn, may interfere with sleeping. Both rumination and disturbed sleep contribute to systemic inflammation (Irwin et al., 2006; Moriarity et al., 2020; Zoccola et al., 2014). Finally, ambitious individuals with elevated reward anticipation may be prone to engaging in health-compromising behaviors that promote inflammation. This is consistent with reported associations of reward hypersensitivity and elevated reward-related brain function with smoking, substance use, and high-fat/high-sugar diets

[1] The observed significant interaction effects between the OFC ($B = 0.386$, $SE = 0.193$, $t = 2.000$, $p = .049$, $\Delta R^2 = 0.036$) or NAc ($B = 0.191$, $SE = 0.086$, $t = 2.233$, $p = .029$, $\Delta R^2 = 0.044$) reward anticipation and ambitious goal-striving tendencies on inflammation hold after removing a history of mood disorder as a covariate. The interaction effects between OFC ($B = -0.031$, $SE = 0.170$, $t = -0.184$, $p = .855$, $\Delta R^2 < 0.001$) or NAc outcome ($B = -0.041$, $SE = 0.069$, $t = -0.589$, $p = .558$, $\Delta R^2 = 0.003$) and ambitious goal-striving tendencies on inflammation remained non-significant after removing a history of mood disorder as a covariate.

(Alloy et al., 2009; Büchel et al., 2017; Gearhardt et al., 2011; Loxton and Tipman, 2017; Nusslock and Miller, 2016; Volkow et al., 2012). Each of these behaviors have been shown to promote inflammation (Bastard et al., 2006; Nettleton et al., 2006; Thomas and Apovian, 2017). Future research is needed to test these possibilities.

Also consistent with hypotheses, individuals with both low ambitious goal-striving tendencies and low NAc neural activity during reward anticipation (but not reward outcome, loss anticipation, or loss outcome) also had higher levels of peripheral inflammation. These relationships were observed after adjusting for BMI, gender, time between assessments, current use of tobacco, prescription anti-inflammatory and psychotropic medications. The results also were comparable with or without a history of a mood disorder or loss-related neural activity as covariates. This suggests that higher levels of ambitious goal-striving tendencies might have buffered individuals with low NAc reward anticipation against mood states that promote inflammation (e.g., learned helplessness and dysphoria). In line with this suggestion, making aspirational goals is associated with a higher sense of well-being (Messersmith and Schulenberg, 2010; Wrosch et al., 2013), and people who are less likely to set ambitious goals on the WASSUP are more likely to have depression (Johnson and Carver, 2006). It makes sense that reward-immune associations are stronger among individuals low in both reward anticipation and ambitious goal-striving tendencies given that such individuals may be particularly prone to dysphoria, learned helplessness, and anhedonia, all of which are associated with inflammation (Felger et al., 2016; Nusslock and Miller, 2016; Osimo et al., 2019). To manage and self-medicate this dysphoria, individuals with both low reward neural activity and goal-striving tendencies may engage in unhealthy behaviors that increase inflammation, such as substance use and high-fat/high-sugar diets (Blum et al., 2000, 2014; Nettleton et al., 2006; O'Connor et al., 2009). In line with this perspective, both conceptual models and empirical findings suggest that low reward-related brain function prospectively predicts problematic substance use behaviors (Blum et al., 2000; Büchel et al., 2017; Nusslock and Miller, 2016; Volkow et al., 2012). Over time, this could generate a positive-feedback circuit whereby low reward neural activity drives inflammation enhancing behaviors, which, in turn, could further reduce reward signaling in the brain, and so on. Future research with longitudinal designs is needed to test these claims. Unexpectedly, we did not detect that individuals with both low ambitious goal-striving tendencies and low OFC neural activity during reward anticipation had high levels of peripheral inflammation.

Collectively, our findings suggest that both low and high sensitivity to rewards can be associated with heightened inflammation. The present study further suggests, however, that ambitious goal-striving tendencies moderate the relationship between reward-related brain function and inflammation. In particular, both individuals with low reward anticipation and low ambitious goal-striving tendencies, as well as individuals with high reward anticipation and high ambitious goal-striving tendencies, displayed more inflammation. This suggests equifinality, whereby either extreme of reward-related brain function may be a risk factor for inflammation, albeit under different conditions of ambitious goal-striving tendencies. Prior work that also examined the link between reward function and inflammation recruited either individuals with mood disorders (e.g., Felger et al., 2016; Haroon et al., 2016) or without mood disorders (e.g., Lasselin et al., 2017; Boyle et al., 2020). By contrast, some of the participants in the current study endorsed a history of mood disorder. It is unclear whether the observed findings would be comparable across individuals with vs. without a mood disorder. However, our analyses (see Footnote) indicated that our primary findings were observed above and beyond the effect of a history of mood disorder, offering preliminary evidence that the findings are not attributable to a mood disorder. Critically, our sample was comprised of healthy young adults with inflammation levels largely within the normal range. However, individuals whose inflammation levels remain chronically high, or increase over time, will be at heightened risk for some health problems across the lifespan (Nusslock and Miller, 2016; Papanicolaou et al., 1998; Willerson and Ridker, 2004). Finally, this work can help us better understand the mechanisms underlying high levels of inflammation in psychiatric conditions, like bipolar spectrum disorders, that are characterized by both high levels of reward responsivity and high goal-striving tendencies (Alloy et al., 2012).

This project has some limitations. First, the cross-sectional, observational nature of its design prevents inferences of causality. A longitudinal study tracking reward-related brain function, goal-striving tendencies, and inflammation is needed. A study like this also could examine the proposed mechanisms (e.g., low positive and high negative mood states, sleep disruption, poor health-related behaviors) through which reward anticipation and goal-striving tendencies affect inflammation. Second, we used a well-validated monetary incentive delay task to examine reward-related brain function. However, preliminary data suggest that inflammation may have a distinct association with reward-signaling to social versus monetary/achievement-oriented rewards (Eisenberger et al., 2017; Irwin et al., 2016; Muscatell et al., 2016). Furthermore, our exploratory results suggest that tendencies to set ambitious social-based goals may be relevant for moderating the relationship between neural reward function and inflammation. Thus, it would be helpful for future research to examine the modulatory effect of the tendencies to set highly ambitious social versus achievement goals on brain-immune signaling to both social and monetary reward cues. Third, for feasibility of data collection for the larger project TEAM, we were unable to fully restrict participants' blood draw visits to a specific time window of the day or request participants to be in a fasting state. The majority of participants completed the blood draw in the afternoon. However, given that immune function can fluctuate depending on time of day and food intake, future work should replicate this work with individuals who are fasting and with blood draws only in the afternoon, during which immune function is more stable. Fourth, because the sample was chosen based on variation in reward responsivity and risk for mood disorders, it is not representative of the general population. Furthermore, it is unclear whether a low score on goal-striving tendencies in the current sample necessarily reflects a "true" low because the sample had excluded a low trait reward sensitivity group. Future research should thus include the entire spectrum of reward sensitivity. Although this constrains the generalizability of the findings, it does not seriously complicate the interpretation of them. Considering that higher levels of ambitious goal-striving tendencies might have provided a buffer from mood states that promote inflammation (e.g., learned helplessness and dysphoria) for individuals with low NAc reward anticipation (Messersmith and Schulenberg, 2010; Wrosch et al., 2013), it makes sense that the association between NAc reward anticipation and inflammation was stronger among individuals with low levels of ambitious goal-striving tendencies. Fifth, relatedly, a low ambitious goal-striving tendency does not necessarily reflect a maladaptive goal regulation style (e.g., low aspiration), but could be realistic goal-striving. Future research should examine goal-striving tendencies that not only consider highly ambitious goals, but also realistic goals, as a moderator for the relationship between reward function and inflammation. Finally, all of the effects reported in the present study were observed with and without correction for a lifetime history of a mood disorder. Nevertheless, it will be important to replicate and extend these findings across the developmental spectrum, and among people at different levels of risk for both mental and physical health conditions.

4.1. Conclusions

Despite these limitations, the present study advances knowledge on neuroimmune signaling in humans. In particular, it demonstrates that goal-striving tendencies moderate the relationship between reward-related brain function and inflammation. It also builds on a growing body of work suggesting that both low and high reward sensitivity are associated with inflammation and highlights the ability to identify

mechanisms to help explain this curvilinear association. These findings advance our understanding of the nuances of neuroimmune signaling and have implications for understanding the pathogenesis of both mental and physical health conditions associated with such signaling.

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.

Acknowledgements

This work was supported by National Institute of Mental Health Grants (NIMH R01 MH077908 and NIMH R01 MH102310) to Lauren B. Alloy. Daniel P. Moriarity was supported by the National Research Service Award F31MH122116 as well as an American Psychological Foundation Visionary Grant. Naoise Mac Giollabhui was supported by the National Research Service Award F31MH118808 as well as an American Psychological Foundation Visionary grant.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2021.03.006.

References

Alloy, L.B., Abramson, L.Y., Walshaw, P.D., Cogswell, A., Grandin, L.D., Hughes, M.E., Iacoviello, B.M., Whitehouse, W.G., Urosevic, S., Nusslock, R., Hogan, M.E., 2008. Behavioral Approach System and Behavioral Inhibition System sensitivities and bipolar spectrum disorders: prospective prediction of bipolar mood episodes. Bipolar Disord. 10 (2), 310–322. https://doi.org/10.1111/bdi.2008.10.issue-210.1111/j.1399-5618.2007.00547.x.

Alloy, L.B., Bender, R.E., Wagner, C.A., Whitehouse, W.G., Abramson, L.Y., Hogan, M.E., Sylvia, L.G., Harmon-Jones, E., 2009. Bipolar spectrum–substance use co-occurrence: behavioral approach system (BAS) sensitivity and impulsiveness as shared personality vulnerabilities. J. Pers. Soc. Psychol. 97 (3), 549–565. https://doi.org/10.1037/a0016061.

Alloy, L.B., Bender, R.E., Whitehouse, W.G., Wagner, C.A., Liu, R.T., Grant, D.A., Jager-Hyman, S., Molz, A., Choi, J.Y., Harmon-Jones, E., Abramson, L.Y., 2012. High behavioral approach system (BAS) sensitivity, reward responsiveness, and goal-striving predict first onset of bipolar spectrum disorders: A prospective behavioral high-risk design. J. Abnormal Psychol. 121 (2), 339–351. https://doi.org/10.1037/a0025877.

Alloy, L.B., Olino, T., Freed, R.D., Nusslock, R., 2016. Role of reward sensitivity and processing in major depressive and bipolar spectrum disorders. Behavior Therapy 47 (5), 600–621. https://doi.org/10.1016/j.beth.2016.02.014.

Argyropoulos, S.V., Nutt, D.J., 2013. Anhedonia revisited: Is there a role for dopamine-targeting drugs for depression? J. Psychopharmacol. 27 (10), 869–877. https://doi.org/10.1177/0269881113494104.

Barlow, M.A., Wrosch, C., McGrath, J.J., 2020. Goal adjustment capacities and quality of life: A meta-analytic review. J. Pers. 88 (2), 307–323. https://doi.org/10.1111/jopy.v88.210.1111/jopy.12492.

Bastard, J.-P., Maachi, M., Lagathu, C., Kim, M.J., Caron, M., Vidal, H., Capeau, J., Feve, B., 2006. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur. Cytokine Netw. 17 (1), 4–12.

Ben-Shaanan, T.L., Azulay-Debby, H., Dubovik, T., Starosvetsky, E., Korin, B., Schiller, M., Green, N.L., Admon, Y., Hakim, F., Shen-Orr, S.S., Rolls, A., 2016. Activation of the reward system boosts innate and adaptive immunity. Nat. Med. 22 (8), 940–944.

Blum, K., Braverman, E.R., Holder, J.M., Lubar, J.F., Monastra, V.J., Miller, D., Lubar, J.O., Chen, T.J., Comings, D.E., 2000. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J. Psychoact. Drugs 32 (Suppl, i–iv), 1–112. https://doi.org/10.1080/02791072.2000.10736099.

Blum, K., Thanos, P.K., Gold, M.S., 2014. Dopamine and glucose, obesity, and reward deficiency syndrome. Front. Psychol. 5 https://doi.org/10.3389/fpsyg.2014.00919.

Boyle, C.C., Stanton, A.L., Eisenberger, N.I., Seeman, T.E., Bower, J.E., 2020. Effects of stress-induced inflammation on reward processing in healthy young women. Brain Behav. Immun. 83, 126–134.

Büchel, C., Peters, J., Banaschewski, T., Bokde, A.L.W., Bromberg, U., Conrod, P.J., Flor, H., Papadopoulos, D., Garavan, H., Gowland, P., Heinz, A., Walter, H., Ittermann, B., Mann, K., Martinot, J.-L., Paillère-Martinot, M.-L., Nees, F., Paus, T., Pausova, Z., Poustka, L., Rietschel, M., Robbins, T.W., Smolka, M.N., Gallinat, J., Schumann, G., Knutson, B., 2017. Blunted ventral striatal responses to anticipated rewards foreshadow problematic drug use in novelty-seeking adolescents. Nat. Commun. 8 (1) https://doi.org/10.1038/ncomms14140.

Capuron, L., Pagnoni, G., Drake, D.F., Woolwine, B.J., Spivey, J.R., Crowe, R.J., Votaw, J.R., Goodman, M.M., Miller, A.H., 2012. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. Arch. Gen. Psychiatry 69 (10), 1044–1053. https://doi.org/10.1001/archgenpsychiatry.2011.2094.

Carver, C.S., White, T.L., 1994. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. J. Pers. Soc. Psychol. 67 (2), 319–333. https://doi.org/10.1037/0022-3514.67.2.319.

Castonguay, A.L., Wrosch, C., Sabiston, C.M., 2014. Systemic inflammation among breast cancer survivors: the roles of goal disengagement capacities and health-related self-protection. Psycho-Oncology 23 (8), 878–885. https://doi.org/10.1002/pon.v23.810.1002/pon.3489.

Cohen, J., Cohen, P., West, S.G., Aiken, L.S., 2013. Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences. Routledge.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9 (1), 46–56. https://doi.org/10.1038/nrn2297.

Dillon, D.G., Holmes, A.J., Jahn, A.L., Bogdan, R., Wald, L.L., Pizzagalli, D.A., 2008. Dissociation of neural regions associated with anticipatory versus consummatory phases of incentive processing. Psychophysiology 45 (1), 36–49. https://doi.org/10.1111/j.1469-8986.2007.00594.x.

Dillon, D.G., Rosso, I.M., Pechtel, P., Killgore, W.D.S., Rauch, S.L., Pizzagalli, D.A., 2014. Peril and pleasure: an RDoC-inspired examination of threat responses and reward processing in anxiety and depression. Depression and Anxiety 31 (3), 233–249. https://doi.org/10.1002/da.2014.31.issue-310.1002/da.22202.

Eisenberger, N.I., Berkman, E.T., Inagaki, T.K., Rameson, L.T., Mashal, N.M., Irwin, M.R., 2010. Inflammation-induced anhedonia: Endotoxin reduces ventral striatum responses to reward. Biol. Psychiatry 68 (8), 748–754. https://doi.org/10.1016/j.biopsych.2010.06.010.

Eisenberger, N.I., Moieni, M., Inagaki, T.K., Muscatell, K.A., Irwin, M.R., 2017. In sickness and in health: the co-regulation of inflammation and social behavior. Neuropsychopharmacology 42 (1), 242–253. https://doi.org/10.1038/npp.2016.141.

Endicott, J., Spitzer, R.L., 1978. A diagnostic interview: The schedule for affective disorders and schizophrenia. Arch. Gen. Psychiatry 35 (7), 837–844.

Felger, J.C., Li, Z., Haroon, E., Woolwine, B.J., Jung, M.Y., Hu, X., Miller, A.H., 2016. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol. Psychiatry 21 (10), 1358–1365. https://doi.org/10.1038/mp.2015.168.

Felger, J.C., Treadway, M.T., 2017. Inflammation effects on motivation and motor activity: role of dopamine. Neuropsychopharmacology 42 (1), 216–241. https://doi.org/10.1038/npp.2016.143.

Forbes, E.E., Rodriguez, E.E., Musselman, S., Narendran, R., 2014. Prefrontal response and frontostriatal functional connectivity to monetary reward in abstinent alcohol-dependent young adults. PloS one 9 (5), e94640. https://doi.org/10.1371/journal.pone.0094640.

Gearhardt, A.N., Yokum, S., Orr, P.T., Stice, E., Corbin, W.R., Brownell, K.D., 2011. Neural correlates of food addiction. Arch. Gen. Psychiatry 68 (8), 808–816. https://doi.org/10.1001/archgenpsychiatry.2011.32.

Haber, S.N., Knutson, B., 2010. The reward circuit: Linking primate anatomy and human imaging. Neuropsychopharmacology 35 (1), 4–26. https://doi.org/10.1038/npp.2009.129.

Haroon, E., Fleischer, C.C., Felger, J.C., Chen, X., Woolwine, B.J., Patel, T., Hu, X.P., Miller, A.H., 2016. Conceptual convergence: increased inflammation is associated with increased basal ganglia glutamate in patients with major depression. Mol. Psychiatry 21 (10), 1351–1357. https://doi.org/10.1038/mp.2015.206.

Haroon, E., Raison, C.L., Miller, A.H., 2012. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. Neuropsychopharmacology 37 (1), 137–162. https://doi.org/10.1038/npp.2011.205.

Harrison, N.A., Voon, V., Cercignani, M., Cooper, E.A., Pessiglione, M., Critchley, H.D., 2016. A neurocomputational account of how inflammation enhances sensitivity to punishments versus rewards. Biol. Psychiatry 80 (1), 73–81. https://doi.org/10.1016/j.biopsych.2015.07.018.

Hotamisligil, G.S., 2006. Inflammation and metabolic disorders. Nature 444 (7121), 860–867. https://doi.org/10.1038/nature05485.

Hughes, J., 2020. reghelper: Helper Functions for Regression Analysis. R package version 0.3.5. https://CRAN.R-project.org/package=reghelper.

Hundt, N.E., Brown, L.H., Kimbrel, N.A., Walsh, M.A., Nelson-Gray, R., Kwapil, T.R., 2013. Reinforcement sensitivity theory predicts positive and negative affect in daily life. Personality Individ. Differ. 54 (3), 350–354.

Hutchinson, M.R., Shavit, Y., Grace, P.M., Rice, K.C., Maier, S.F., Watkins, L.R., Barker, E.L., 2011. Exploring the neuroimmunopharmacology of opioids: an integrative review of mechanisms of central immune signaling and their implications for opioid analgesia. Pharmacol. Rev. 63 (3), 772–810. https://doi.org/10.1124/pr.110.004135.

Inagaki, T.K., Muscatell, K.A., Irwin, M.R., Moieni, M., Dutcher, J.M., Jevtic, I., Breen, E.C., Eisenberger, N.I., 2015. The role of the ventral striatum in inflammatory-induced approach toward support figures. Brain Behav. Immun. 44, 247–252. https://doi.org/10.1016/j.bbi.2014.10.006.

Irwin, M.R., Cole, S.W., 2011. Reciprocal regulation of the neural and innate immune systems. Nat. Rev. Immunol. 11 (9), 625–632. https://doi.org/10.1038/nri3042.

Irwin, M.R., Olmstead, R., Carroll, J.E., 2016. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. Biol. Psychiatry 80 (1), 40–52. https://doi.org/10.1016/j.biopsych.2015.05.014.

Irwin, M.R., Wang, M., Campomayor, C.O., Collado-Hidalgo, A., Cole, S., 2006. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. Arch. Intern. Med. 166 (16), 1756–1762. https://doi.org/10.1001/archinte.166.16.1756.

Johnson, S.L., Carver, C.S., 2006. Extreme goal setting and vulnerability to mania among undiagnosed young adults. Cognitive Therapy Res. 30 (3), 377–395. https://doi.org/10.1007/s10608-006-9044-7.

Kaptoge, S., Seshasai, S.R.K., Gao, P., Freitag, D.F., Butterworth, A.S., Borglykke, A., Di Angelantonio, E., Gudnason, V., Rumley, A., Lowe, G.D.O., Jorgensen, T., Danesh, J., 2014. Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. Eur. Heart J. 35 (9), 578–589. https://doi.org/10.1093/eurheartj/eht367.

Kelley, N.J., Kramer, A.M., Young, K.S., Echiverri-Cohen, A.M., Chat, I.-K.-Y., Bookheimer, S.Y., Nusslock, R., Craske, M.G., Zinbarg, R.E., 2019. Evidence for a general factor of behavioral activation system sensitivity. J. Res. Pers. 79, 30–39. https://doi.org/10.1016/j.jrp.2019.01.002.

Lacourt, T.E., Vichaya, E.G., Chiu, G.S., Dantzer, R., Heijnen, C.J., 2018a. The high costs of low-grade inflammation: persistent fatigue as a consequence of reduced cellular-energy availability and non-adaptive energy expenditure. Front. Behav. Neurosci. 12, 78.

Lacourt, T.E., Vichaya, E.G., Escalante, C., Manzullo, E.F., Gunn, B., Hess, K.R., Heijnen, C.J., Dantzer, R., 2018b. An effort expenditure perspective on cancer-related fatigue. Psychoneuroendocrinology 96, 109–117.

Lasselin, J., Treadway, M.T., Lacourt, T.E., Soop, A., Olsson, M.J., Karshikoff, B., Paues-Göranson, S., Axelsson, J., Dantzer, R., Lekander, M., 2017. Lipopolysaccharide alters motivated behavior in a monetary reward task: a randomized trial. Neuropsychopharmacology 42 (4), 801–810. https://doi.org/10.1038/npp.2016.191.

Libby, P., Ridker, P.M., Hansson, G.K., Network, L.T., on Atherothrombosis., 2009. Inflammation in atherosclerosis: from pathophysiology to practice. J. Am. Coll. Cardiol. 54 (23), 2129–2138. https://doi.org/10.1016/j.jacc.2009.09.009.

Loxton, N.J., Tipman, R.J., 2017. Reward sensitivity and food addiction in women. Appetite 115, 28–35. https://doi.org/10.1016/j.appet.2016.10.022.

Mac Giollabhui, N., Ng, T.H., Ellman, L.M., Alloy, L.B., 2020. The longitudinal associations of inflammatory biomarkers and depression revisited: systematic review, meta-analysis, and meta-regression. Mol. Psychiatry 1–13.

Mantovani, A., Allavena, P., Sica, A., Balkwill, F., 2008. Cancer-related inflammation. Nature 454 (7203), 436–444. https://doi.org/10.1038/nature07205.

McCabe, C., Woffindale, C., Harmer, C.J., Cowen, P.J., 2012. Neural processing of reward and punishment in young people at increased familial risk of depression. Biol. Psychiatry 72 (7), 588–594.

McMurray, M.S., Amodeo, L.R., Roitman, J.D., 2016. Consequences of adolescent ethanol consumption on risk preference and orbitofrontal cortex encoding of reward. Neuropsychopharmacology 41 (5), 1366–1375.

Messersmith, E.E., Schulenberg, J.E., 2010. Goal attainment, goal striving, and well-being during the transition to adulthood: a ten-year U.S. national longitudinal study: life goal completion. New Dir. Child Adolesc. Dev. 2010 (130), 27–40. https://doi.org/10.1002/cd.279.

Meyer, B., Johnson, S.L., Winters, R., 2001. Responsiveness to threat and incentive in bipolar disorder: relations of the bis/bas scales with symptoms. J. Psychopathol. Behav. Assessment 23 (3), 133–143. https://doi.org/10.1023/A:1010929402770.

Miller, A.H., Haroon, E., Raison, C.L., Felger, J.C., 2013. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depression and Anxiety 30 (4), 297–306. https://doi.org/10.1002/da.2013.30.issue-410.1002/da.22084.

Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. Psychiatry 65 (9), 732–741. https://doi.org/10.1016/j.biopsych.2008.11.029.

Miller, G.E., Chen, E., Parker, K.J., 2011. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol. Bull. 137 (6), 959–997. https://doi.org/10.1037/a0024768.

Miller, G.E., Cole, S.W., 2012. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. Biol. Psychiatry 72 (1), 34–40. https://doi.org/10.1016/j.biopsych.2012.02.034.

Miller, G.E., Wrosch, C., 2007. You've gotta know when to fold 'em: goal disengagement and systemic inflammation in adolescence. Psychol. Sci. 18 (9), 773–777.

Modabbernia, A., Taslimi, S., Brietzke, E., Ashrafi, M., 2013. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biol. Psychiatry 74 (1), 15–25. https://doi.org/10.1016/j.biopsych.2013.01.007.

Moieni, M., Tan, K.M., Inagaki, T.K., Muscatell, K.A., Dutcher, J.M., Jevtic, I., Breen, E. C., Irwin, M.R., Eisenberger, N.I., 2019. Sex differences in the relationship between inflammation and reward sensitivity: a randomized controlled trial of endotoxin. Biological Psychiatry 4 (7), 619–626. https://doi.org/10.1016/j.bpsc.2019.03.010.

Moriarity, D.P., Ng, T., Titone, M.K., Chat, I.K.-Y., Nusslock, R., Miller, G.E., Alloy, L.B., 2020. Reward responsiveness and ruminative styles interact to predict inflammation and mood symptomatology. Behav. Ther. 51 (5), 829–842.

Munkholm, K., Braüner, J.V., Kessing, L.V., Vinberg, M., 2013. Cytokines in bipolar disorder vs. healthy control subjects: a systematic review and meta-analysis. J. Psychiatr. Res. 47 (9), 1119–1133. https://doi.org/10.1016/j.jpsychires.2013.05.018.

Muscatell, K.A., Moieni, M., Inagaki, T.K., Dutcher, J.M., Jevtic, I., Breen, E.C., Irwin, M. R., Eisenberger, N.I., 2016. Exposure to an inflammatory challenge enhances neural sensitivity to negative and positive social feedback. Brain Behav. Immun. 57, 21–29. https://doi.org/10.1016/j.bbi.2016.03.022.

Nestor, L.J., McCabe, E., Jones, J., Clancy, L., Garavan, H., 2018. Smokers and ex-smokers have shared differences in the neural substrates for potential monetary gains and losses. Addiction biology 23 (1), 369–378. https://doi.org/10.1111/adb.12484.

Nettleton, J.A., Steffen, L.M., Mayer-Davis, E.J., Jenny, N.S., Jiang, R., Herrington, D.M., Jacobs, D.R., 2006. Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA). Am. J. Clin. Nutr. 83 (6), 1369–1379. https://doi.org/10.1093/ajcn/83.6.1369.

Nusslock, R., Alloy, L.B., 2017. Reward processing and mood-related symptoms: An RDoC and translational neuroscience perspective. , *216*, 3-16. Journal of Affective Disorders 216, 3–16. https://doi.org/10.1016/j.jad.2017.02.001.

Nusslock, R., Almeida, J.R., Forbes, E.E., Versace, A., Frank, E., LaBarbara, E.J., Klein, C. R., Phillips, M.L., 2012. Waiting to win: elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar disorder adults. Bipolar disorders 14 (3), 249–260. https://doi.org/10.1111/j.1399-5618.2012.01012.x.

Nusslock, R., Miller, G.E., 2016. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. Biol. Psychiatry 80 (1), 23–32. https://doi.org/10.1016/j.biopsych.2015.05.017.

O'Connor, M.-F., Bower, J.E., Cho, H.J., Creswell, J.D., Dimitrov, S., Hamby, M.E., Hoyt, M.A., Martin, J.L., Robles, T.F., Sloan, E.K., Thomas, K.S., Irwin, M.R., 2009. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. Brain Behav. Immun. 23 (7), 887–897. https://doi.org/10.1016/j.bbi.2009.04.005.

Odegaard, J.I., Chawla, A., 2013. Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. Science (New York, N.Y.) 339 (6116), 172–177. https://doi.org/10.1126/science.1230721.

Osimo, E.F., Baxter, L.J., Lewis, G., Jones, P.B., Khandaker, G.M., 2019. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychol. Med. 49 (12), 1958–1970. https://doi.org/10.1017/S0033291719001454.

Pace, T.W.W., Miller, A.H., 2009. Cytokines and glucocorticoid receptor signaling. Relevance to major depression. Ann. N. Y. Acad. Sci. 1179, 86–105. https://doi.org/10.1111/j.1749-6632.2009.04984.x.

Papanicolaou, D.A., Wilder, R.L., Manolagas, S.C., Chrousos, G.P., 1998. The pathophysiologic roles of interleukin-6 in human disease. Ann. Internal Med. 128 (2), 127–137. https://doi.org/10.7326/0003-4819-128-2-199801150-00009.

Pizzagalli, D.A., 2014. Depression, stress, and anhedonia: toward a synthesis and integrated model. Annu. Rev. Clin. Psychol. 10 (1), 393–423. https://doi.org/10.1146/annurev-clinpsy-050212-185606.

Raison, C.L., Miller, A.H., 2003. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. Am. J. Psychiatry 160 (9), 1554–1565. https://doi.org/10.1176/appi.ajp.160.9.1554.

Revelle, W. (2019). psych: Procedures for Personality and Psychological Research, Northwestern University, Evanston, Illinois, USA, https://CRAN.R-project.org/package=psych Version = 1.9.12.

Ridker, P.M., 2007. Inflammatory biomarkers and risks of myocardial infarction, stroke, diabetes, and total mortality: implications for longevity. Nutr. Rev. 65 (12 Pt 2), S253–S259. https://doi.org/10.1111/j.1753-4887.2007.tb00372.x.

Rolls, E.T., Cheng, W., Du, J., Wei, D., Qiu, J., Dai, D., et al., 2020. Functional connectivity of the right inferior frontal gyrus and orbitofrontal cortex in depression. Social cognitive and affective neuroscience, 15(1), 75-86.

Rosenblat, J.D., Cha, D.S., Mansur, R.B., McIntyre, R.S., 2014. Inflamed moods: A review of the interactions between inflammation and mood disorders. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 53, 23–34. https://doi.org/10.1016/j.pnpbp.2014.01.013.

Samanez-Larkin, G.R., Gibbs, S.E.B., Khanna, K., Nielsen, L., Carstensen, L.L., Knutson, B., 2007. Anticipation of monetary gain but not loss in healthy older adults. Nat. Neurosci. 10 (6), 787–791. https://doi.org/10.1038/nn1894.

Schiller, M., Ben-Shaanan, T.L., Rolls, A., 2021. Neuronal regulation of immunity: why, how and where? Nat. Rev. Immunol. 21 (1), 20–36.

Scrivo, R., Vasile, M., Bartosiewicz, I., Valesini, G., 2011. Inflammation as "common soil" of the multifactorial diseases. Autoimmun. Rev. 10 (7), 369–374. https://doi.org/10.1016/j.autrev.2010.12.006.

Sherdell, L., Waugh, C.E., Gotlib, I.H., 2012. Anticipatory pleasure predicts motivation for reward in major depression. J. Abnorm. Psychol. 121 (1), 51–60. https://doi.org/10.1037/a0024945.

Stewart, J.C., Rand, K.L., Muldoon, M.F., Kamarck, T.W., 2009. A prospective evaluation of the directionality of the depression–inflammation relationship. Brain Behav. Immun. 23 (7), 936–944. https://doi.org/10.1016/j.bbi.2009.04.011.

Tan, J.-C., 2015. probemod: Statistical Tools for Probing Moderation Effects. R package version 0.2.1. https://CRAN.R-project.org/package=probemod.

Thomas, D., Apovian, C., 2017. Macrophage functions in lean and obese adipose tissue. Metabolism 72, 120–143. https://doi.org/10.1016/j.metabol.2017.04.005.

Torrubia, R., Ávila, C., Moltó, J., Caseras, X., 2001. The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Personality Individ. Differ. 31 (6), 837–862. https://doi.org/10.1016/S0191-8869(00)00183-5.

Volkow, N.D., Wang, G.J., Fowler, J.S., Tomasi, D., Baler, R., 2012. Food and drug reward: overlapping circuits in human obesity and addiction. Curr. Topics Behav. Neurosci. 11, 1–24. https://doi.org/10.1007/7854_2011_169.

Weber, M.D., Godbout, J.P., Sheridan, J.F., 2017. Repeated social defeat, neuroinflammation, and behavior: monocytes carry the signal. Neuropsychopharmacology 42 (1), 46–61. https://doi.org/10.1038/npp.2016.102.

Wickham, H., 2016. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag, New York.
Wickham, H., Miller, E., 2019. haven: Import and Export 'SPSS', 'Stata' and 'SAS' Files. R package version 2.2.0. https://CRAN.R-project.org/package=haven.
Willerson, J.T., Ridker, P.M., 2004. Inflammation as a cardiovascular risk factor. Circulation, 109(21_suppl_1), II–2. 10.1161/01.CIR.0000129535.04194.38.
Wrosch, C., Miller, G.E., Scheier, M.F., Brun De Pontet, S., 2007. Giving up on unattainable goals: benefits for health? Personality and Social Psychology Bulletin, 33, 251–265.
Wrosch, C., Scheier, M.F., Miller, G.E., 2013. Goal adjustment capacities, subjective well-being, and physical health. Soc. Pers. Psychol. Compass 7 (12), 847–860. https://doi.org/10.1111/spc3.12074.
Wrosch, C., Scheier, M.F., Miller, G.E., Schulz, R., Carver, C.S., 2003. Adaptive self-regulation of unattainable goals: goal disengagement, goal reengagement, and subjective well-being. Personality Social Psychol. Bull. 29 (12), 1494–1508. https://doi.org/10.1177/0146167203256921.
Yuan, N., Chen, Y., Xia, Y., Dai, J., Liu, C., 2019. Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. Transl. Psychiatry 9 (1), 1–13. https://doi.org/10.1038/s41398-019-0570-y.
Zoccola, P.M., Figueroa, W.S., Rabideau, E.M., Woody, A., Benencia, F., 2014. Differential effects of poststressor rumination and distraction on cortisol and C-reactive protein. Health Psychology 33 (12), 1606–1609. https://doi.org/10.1037/hea0000019.