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Association Between Interleukin-6 and Striatal Prediction-Error Signals Following Acute Stress in Healthy Female Participants

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ABSTRACT

BACKGROUND: Stress is widely known to alter behavioral responses to rewards and punishments. It is believed that stress may precipitate these changes through modulation of corticostriatal circuitry involved in reinforcement learning and motivation, although the intervening mechanisms remain unclear. One candidate is inflammation, which can rapidly increase following stress and can disrupt dopamine-dependent reward pathways.

METHODS: Here, in a sample of 88 healthy female participants, we first assessed the effect of an acute laboratory stress paradigm on levels of plasma interleukin-6 (IL-6), a cytokine known to be both responsive to stress and elevated in depression. In a second laboratory session, we examined the effects of a second laboratory stress paradigm on reward prediction error (RPE) signaling in the ventral striatum.

RESULTS: We show that individual differences in stress-induced increases in IL-6 (session 1) were associated with decreased ventral striatal RPE signaling during reinforcement learning (session 2), though there was no main effect of stress on RPE. Furthermore, changes in IL-6 following stress predicted intraindividual variability in perceived stress during a 4-month follow-up period.

CONCLUSIONS: Taken together, these data identify a novel link between IL-6 and striatal RPEs during reinforcement learning in the context of acute psychological stress, as well as future appraisal of stressful life events.

Keywords: Inflammation, Interleukin-6, Reinforcement learning, Reward prediction error, Stress, Ventral striatum

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Stress is a major risk factor for psychiatric disorders (1–3), though its effects are not fully understood. Stress exposure can initiate a neuroendocrine cascade that modulates how individuals perceive and respond to rewarding or threatening cues in their environment (4–11). Specifically, it has been shown that stress may reduce acquisition of reward-related information (8,12,13) as well as disrupt normal reinforcer devaluation (9,14,15), two phenomena that are commonly observed in stress-related psychiatric disorders (16–20).

In animal models, substantial research has suggested that stress may induce these behavioral changes to rewarding stimuli via effects on the mesocorticolimbic dopamine (DA) system. Acute stressors transiently increase DA release in the nucleus accumbens (NAcc) while also promoting longer-term DAergic increases in the medial prefrontal cortex (10,21–23). Interestingly, more recent studies have suggested that stress may have selective effects on DAergic responses to reward receipt (24), raising the possibility that behavioral changes to reinforcers may be mediated by the effects of stress on DAergic reward prediction error (RPE) signaling, a core mechanism of reinforcement learning (RL) (25,26).

While early research on the relationship among stress, DAergic function, and subsequent behavioral changes focused on the role of the hypothalamic-pituitary-adrenal axis (27), recent work has increasingly recognized an important role for stress-induced immune responses (28–31). As with glucocorticoids, proinflammatory cytokines such as interleukin-6 (IL-6), IL-1, and tumor necrosis factor alpha can be stimulated by acute stress exposure (32–34). Behaviorally, acute administration of these proinflammatory cytokines has been shown to reduce sensitivity to rewards while augmenting sensitivity to punishment (35), a pattern that is consistent with evolutionary models (31) and matches the effects of acute stress (12,13,36) [though see also (6,37,38)]. Importantly, only IL-6 has been reliably shown in meta-analyses to be both elevated in depression (39–42) and sensitive to laboratory measures of acute stress (33), and it is increasingly recognized as a playing an important role in mood disorders (43).

A growing body of evidence suggests that DA and cytokines may influence each other through multiple pathways. Both acute and chronic treatment with cytokine inducers—including direct administration of IL-6—has been shown to disrupt DA synaptic availability and synthesis in rodents (44–46), nonhuman primates (47,48), and humans (49). Similarly, in human functional neuroimaging studies, both chronic and acute administration of cytokine inducers has been

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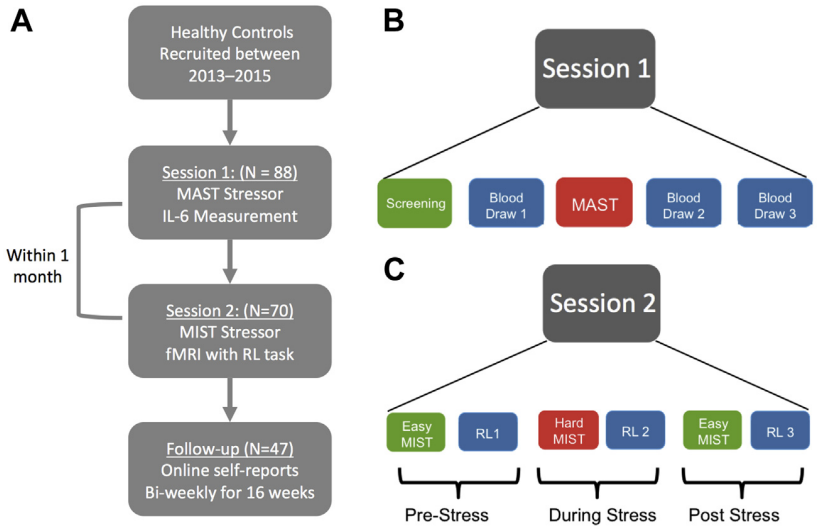

Figure 1. Schematic diagram illustrating the design of study sessions 1 and 2. **(A)** Overall flow of participants through the study. **(B)** During session 1, participants first completed a Structured Clinical Interview for DSM and other screening measures (see Methods and Materials), a baseline blood draw, and then the Maastricht Acute Stress Task (MAST) laboratory stress challenge. Following the MAST, two other blood draws were collected. **(C)** During session 2, participants completed a functional magnetic resonance imaging (fMRI) scanning session in which they had to complete blocks of a reinforcement learning (RL) task that were interleaved between easy and hard (stressful) blocks of the Montreal Imaging Stress Task (MIST). For each of the three stress conditions (prestress, during stress, poststress), runs of the MIST and RL were completed twice. IL-6, interleukin-6.

associated with blunted ventral striatal responses to reward anticipation (49,50), prediction-error signaling during RL (35), and novelty-driven activity in the DAergic midbrain (51). Alternatively, however, there is also growing evidence that DA signaling may modulate cytokine responses. DA receptors have been identified on numerous components of the innate immune system (52), including lymphocytes and T cells. These studies have largely suggested that DA acts to inhibit the actions of activated T cells. In particular, DA receptor D2 knockout mice show a remarkable anti-inflammatory response, suggesting that DA signaling may be primarily anti-inflammatory in nature (53,54), though not in all cases (52).

Given these potentially bidirectional pathways between inflammation on DA signaling pathways, we predicted that stress-induced increases in inflammatory cytokines would be associated with a reduction in DA-dependent RPE signals during RL. To date, however, no study has tested the relationship between stress-induced IL-6 and stress-related changes in striatal prediction error signaling and whether these mechanisms predict future levels of stress appraisal.

In the present study, we sought to address these questions through a combination of laboratory stress challenges, plasma measures of IL-6, and functional neuroimaging in a sample of 88 healthy female participants assessed across two study visits (Figure 1). Only women were investigated owing to elevated prevalence of depression in female subjects (55), as well as significant sex differences in psychological and hormonal responses to stress (56) that could substantially reduce our power to detect individual differences. During the first session, participants were exposed to the Maastricht Acute Stress Task (MAST) (57), a robust laboratory stress paradigm, while blood was sampled intravenously. During the second session, participants completed a functional neuroimaging session that included functional runs of an RL task (58) interleaved with blocks of a well-validated neuroimaging stress paradigm, the Montreal Imaging Stress Task (MIST) (59). Effects of both stressors on mood were assessed using visual analog mood scales (VAMS) (60). We hypothesized that larger increases in IL-6 following stress (as assessed in the first behavioral session) would predict a greater blunting of RPE signals during stress (as assessed in the second session). After these laboratory visits, participants were followed for a period of 4 months to assess self-reported stressful experiences in daily life. For these assessments, we predicted that greater biological responses to laboratory stressors would predict self-reported stressful experiences during the follow-up period.

METHODS AND MATERIALS

Participants and Study Description

A total of 88 healthy female participants were included in this study. For details on participant eligibility criteria, see Supplemental Methods. All recruitment and testing procedures were approved by the Partners Institutional Review Board. The study comprised two laboratory visits followed by a 4-month period of self-report questions administered online every 2 weeks. Details of study procedures can be found in Supplemental Methods. Subject demographic characteristics are summarized in Supplemental Table S1.

Session 1: MAST Laboratory Stressor

To induce stress during the first session, participants completed the MAST (57). The MAST is a laboratory stress paradigm that combines alternating periods of well-validated stress-inducing procedures including a cold pressor and performance of serial subtraction in front of evaluators. For details of the MAST administration, see Supplemental Methods.

Session 1: Sample Collection and Analysis

To assess IL-6 responses, plasma samples were drawn intravenously at −10 minutes (before stressor), +45 minutes following stressor, and +90 minutes following stressor. To assess salivary cortisol, saliva samples were collected at six time points: −110 minutes (before stressor), −30 minutes, immediately before stressor, +20 minutes following stressor, +35 minutes, and +80 minutes. For details of collection and analysis, see Supplemental Methods.

Session 2: Laboratory Stressor

For the session 2 laboratory stressor (Figure 1), which was performed during a functional magnetic resonance imaging scan, we used a modified version of the MIST (59), a widely used and well-validated stress paradigm. Briefly, this task requires participants to solve arithmetic problems while their performance is publicly evaluated. For details of the MIST administration, see Supplemental Methods. To assess salivary cortisol during session 2, saliva samples were collected at four time points: before entry into the scanner, 3 minutes before onset of stress blocks, +25 minutes after the onset of the stress blocks, and +40 minutes after the onset of the stress blocks.

Reinforcement Learning Task

To assess RPE signals, participants were asked to complete a well-validated instrumental conditioning paradigm (58). Details of the task are presented in Supplemental Methods. Briefly, subjects were instructed to choose between two visual stimuli displayed on a screen. Each of the stimuli in the pairs was associated with either an 80% or 20% probability of a given outcome (gain: win $1 or $0; loss: lose $1 or $0; neutral: look at gray square or nothing). There were a total of six RL runs across the experiment, with two runs for each stress condition (prestress, during stress, poststress).

Primary analysis focused on a parametric modulation contrast for RPE signals extracted from an anatomically defined NAcc mask. For details on the computational model, neuroimaging acquisition, processing and region-of-interest (ROI) analysis, see the Supplement.

Follow-up Period

To examine the ecological validity of biological responses to laboratory stressors, all participants were asked to complete online self-report questionnaires every 2 weeks for a 4-month follow-up period. Our primary measure of interest was the Perceived Stress Scale (PSS) (61), which was used to assess ongoing perceptions of stress in daily life. We examined both mean level of perceived stress and variability over time. To assess variability, we calculated mean sum of squared differences, a standard metric used to capture variability in symptom experience (62).

RESULTS

Session 1: Effects of Acute Stress on Plasma IL-6 and Salivary Cortisol

Using a three (time points) repeated-measures analysis of variance (ANOVA), we found that the MAST induced a significant increase in plasma IL-6 ($F_{1.43,92}$ = 17.89, p = 8.0 × 10^{-6}; η_p^2 = .28) (Figure 2). This effect remained highly significant when controlling for menstrual cycle phase (70% follicular; 30% luteal) ($F_{1.43,90}$ = 16.77, p = 1.6 × 10^{-5}; η_p^2 = .27), and there was no time points × menstrual cycle phase interaction ($F_{1.43,90}$ = 0.89, p = .384). There was, however, a main effect of cycle phase such that participants in the luteal phase had lower levels of IL-6 than those in the follicular phase ($F_{1,45}$ = 5.24, p = .027; η_p^2= .10). Given prior studies (63), we also examined whether body mass index was

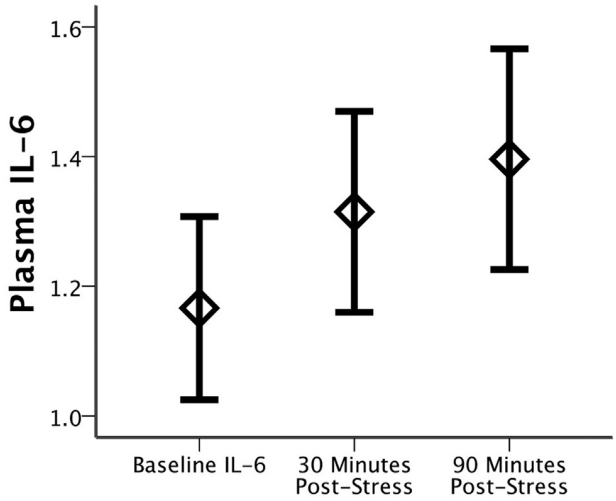

Figure 2. Change in plasma interleukin-6 (IL-6) levels (raw values) following the Maastricht Acute Stress Task. Error bars represent SE.

associated with change in IL-6, but we did not find an association between body mass index and change in IL-6 following stress (see Supplemental Table S2). Baseline PSS scores were also unrelated to change in IL-6 levels (Spearman ρ = .10, p = .466), though we did observe baseline associations with the State-Trait Anxiety Inventory (see Supplement).

Additionally, using a six (time points) repeated-measures ANOVA, we found that the MAST produced a significant increase in salivary cortisol ($F_{2.34,182.38}$ = 27.87, p = 1.5 × 10^{-12}), with a strong quadratic effect ($F_{1,78}$ = 33.14, p = 1.62 × 10^{-7}) (see Supplemental Figure S1).

Session 1: Effects of Acute Stress on Mood and Relationships to IL-6

Using an 8 (time points) x 5 (questions) repeated-measures ANOVA, we found that the MAST stressor during session 1 induced a significant overall change in mood ($F_{3.28,553}$ = 70.78, p = 1.78 × 10^{-35}), with the expected quadratic effect ($F_{1,79}$ = 125.05, p = 5.98 × 10^{-18}) showing an increase in negative mood following the stressor (Figure 3A). This quadratic effect remained significant when controlling for menstrual cycle phase ($F_{1,77}$ = 30.56, p = 4.26 × 10^{-7}), and there was no interaction between this quadratic effect and menstrual cycle phase ($F_{1,77}$ = 0.064, p = .801). For each individual VAMS question, quadratic effects revealed that immediately following the MAST participants felt less happy ($F_{1,80}$ = 113.84, p = 4.87 × 10^{-17}), relaxed ($F_{1,80}$ = 98.01, p = 1.51 × 10^{-15}), friendly ($F_{1,80}$ = 114.65, p = 4.11 × 10^{-17}), sociable ($F_{1,80}$ = 66.79, p = 3.71 × 10^{-12}), and quick witted ($F_{1,80}$ = 67.08, p = 3.71 × 10^{-12}).

There were no relationships among change in IL-6 levels in response to the MAST and change in mood ratings as assessed by any of the five VAMS questions: (happy: Spearman ρ = .06, p = .663; relaxed: Spearman ρ = .13, p = .345; friendly: Spearman ρ = .10, p = .473; sociable: Spearman ρ = .001, p = .992; quick witted: Spearman ρ = .02, p = .868).

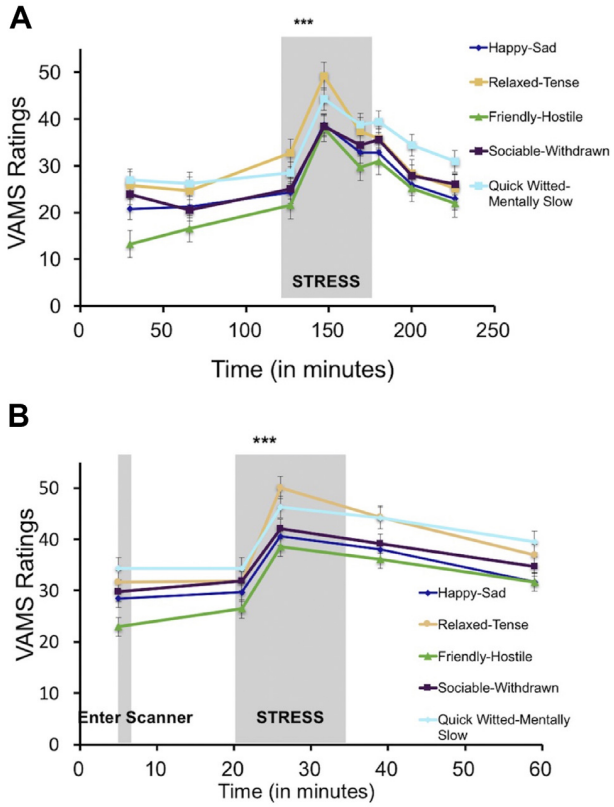

Figure 3. Stress manipulations increase negative affect. **(A)** In session 1, the Maastricht Acute Stress Task induced a significant increase in negative affect across all five visual analog mood scales (VAMS) questions (happy-sad, relaxed-tense, friendly-hostile, sociable-withdrawn, quick witted–mentally slow). **(B)** Similarly, in session 2, the Montreal Imaging Stress Task also induced a significant decrease in mood across all five VAMS questions. All VAMS items are scored such that higher scores indicate more negative affect.

Session 2: Effects of Acute Stress on Mood and Salivary Cortisol

Using a 5 (time points) × 5 (questions) repeated-measures ANOVA, we found that the MIST stressor during session 2 also induced a significant overall decrease in mood ($F_{2.05,260}$ = 50.65, $p = 2.46 \times 10^{-17}$) with a quadratic effect ($F_{1,65}$ = 67.85, $p = 1.10 \times 10^{-11}$) (Figure 3B). This quadratic effect remained significant when controlling for menstrual cycle phase ($F_{1,61}$ = 7.28, p = .009), and there was no interaction between this quadratic effect and menstrual cycle phase ($F_{1,61}$ = 0.003, p = .960). Specifically, immediately following the MIST participants reported feeling less happy ($F_{1,65}$ = 46.60, $p = 3.51 \times 10^{-9}$), relaxed ($F_{1,65}$ = 39.75, $p = 2.88 \times 10^{-8}$), friendly ($F_{1,65}$ = 62.92, $p = 3.85 \times 10^{-11}$), sociable ($F_{1,65}$ = 36.48, $p = 8.27 \times 10^{-8}$), and quick witted ($F_{1,65}$ = 24.56, $p = 5.0 \times 10^{-6}$). In addition to these main effects, individual differences in mood responses to stress were significantly correlated between the MAST (session 1) and MIST (session 2) stressors for all five questions (happy: Pearson r = .48, p = .0002; relaxed: r = .31, p = .019; friendly: r = .35, p = .007; sociable: r = .38, p = .004; quick witted: r = .46, p = .0004).

For salivary cortisol, a three (time points) repeated-measures ANOVA revealed no main effect of the MIST stressor on cortisol ($F_{1.71,116.06}$ = 21.31, p = .437) (see Supplemental Figure S1). This null result was driven by the absence of a positive cortisol response in approximately one half of the participants, which is consistent with other studies using the MIST (59,64). Importantly however, the percentage of change in cortisol from prestress to poststress during session 1 was positively correlated with the percentage of change in cortisol from prestress to poststress during session 2 (Pearson r = .40, p = .006).

Session 2: Effects of Acute Stress on Behavioral Performance

A 2 (valence: win/loss) × 3 (stress condition: prestress, during stress, poststress) × 2 (run number) repeated-measures ANOVA with menstrual cycle phase included as a between-groups variable revealed a main effect of the stress condition such that performance accuracy increased over the course of the experiment ($F_{2,106}$ = 3.30, p = .041). There was no main effect of valence (win/loss) ($F_{1,53}$ = 2.5, p = .120) nor stress condition ×valence interaction ($F_{2,106}$ = 1.60, p = .21), though follow-up Student t tests did reveal a significant improvement in performance on loss trials during stress as opposed to prestress (t_{62} = 2.96, p = .004), with no change in accuracy for win trials (t_{62} = 0.20, p = .842).

There was no main effect of menstrual cycle phase, nor any interactions with menstrual cycle phase and stress condition, though there was a significant interaction between menstrual cycle phase and valence ($F_{1,52}$ = 7.94, p = .007) such that women in the luteal phase showed a greater overall accuracy for win trials relative to loss trials, while women in the follicular phase showed little difference between the two.

Session 2: Prediction Error Signaling

Averaging across all RL sessions, we observed a main effect of positive RPE signals in the NAcc using a small volume correction with a bilateral NAcc anatomical mask drawn from the Harvard-Oxford probabilistic atlas (small volume correction left NAcc: x = −6, y = 10, z = −6, t = 5.25, familywise error p = .0005; small volume correction right NAcc: x = 8, y = 6, z = −4, t = 4.69, familywise error p = .003) (Figure 4A). For negative RPE, a whole-brain analysis revealed significant activity in bilateral anterior insula and areas of dorsal anterior cingulate and dorsomedial prefrontal cortex (for a full list of regions identified by RPE contrasts, see Supplemental Table S3). There was no main effect (linear or quadratic) of the MIST stress manipulation on the magnitude of positive or negative RPE signals. Consistent with prior studies (58,65), the strength of positive RPE signals in the NAcc was positively associated with performance accuracy across win and loss trials accuracy (see Supplement).

Session 2: Stress-Induced Change in RPE Signals and IL-6 (Assessed in Session 1)

Using extracted RPE β weights from an anatomically defined NAcc ROI, we examined the relationships between change in IL-6 during stress (assessed in session 1) and change in NAcc RPE β weights following stress (assessed in session 2). We

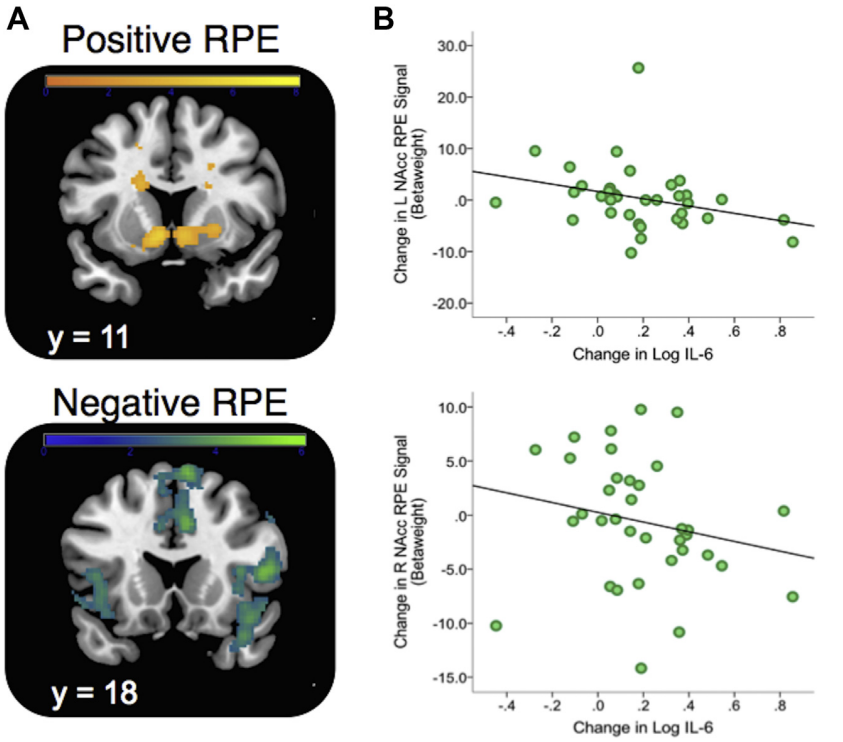

Figure 4. Positive and negative reward prediction error (RPE) signals during reinforcement learning and relationship to stress-induced change in interleukin-6 (IL-6). **(A)** Model-based PE signals averaged across all three stress conditions (prestress, during stress, and poststress) and found to predict activity in ventral striatum (positive RPE) and bilateral insula/dorsal anterior cingulate cortex (negative RPE). All reported regions were corrected for multiple comparisons. Activation patterns are shown using an uncorrected height threshold of $t > 2.5$ for visualization purposes. **(B)** Association between stress-induced change in left (L) (top) and right (R) (bottom) nucleus accumbens (NAcc) positive RPE β weight (RPE contrast: prestress – during stress) and change in plasma IL-6 following stress. Note: Extracted values for right and left NAcc regions of interest were defined anatomically to avoid statistical nonindependence (see Methods and Materials). Note that for L NAcc, one subject was a univariate outlier ($Z = 4.38$), but the association with change in IL-6 was unaltered when including ($r = -.39$, $p = .019$) or excluding this subject ($r = -.42$, $p = .014$).

observed an inverse relationship such that larger increases in IL-6 following stress at times 2 and 3 were associated with larger decreases in NAcc RPE β weights following stress (see Table 1 and Figure 4B). This effect was strongest in the left NAcc for the comparison of prestress > poststress RPE signals. Importantly, the association between IL-6 and RPE remained when controlling for change in cortisol ($\beta = -0.60$, $t = -3.54$, $p = .002$). This targeted ROI analysis was also followed by a whole-brain analysis for both positive and negative RPE contrasts, but no region showed a significant association after controlling for multiple comparisons. There were no significant associations with baseline IL-6 and NAcc RPE across the prestress, during-stress, and poststress time points, though these associations were not significantly different from the correlations observed using difference scores (see Supplemental Table S4).

Table 1. Spearman Correlations Between Stress-Induced Change in IL-6 and Change in Striatal RPE Signals

	Log IL-6 Increase Time 1 to Time 2	Log IL-6 Increase Time 1 to Time 3
Change in L NAcc RPE From Prestress to During Stress	−0.08	−0.10
Change in R NAcc RPE From Prestress to During Stress	−0.21	−0.34[a]
Change in L NAcc RPE From Prestress to Poststress	−0.39[b]	−0.39[a]
Change in R NAcc RPE From Prestress to Poststress	0.04	−0.16

IL-6, interleukin-6; L, left; NAcc, nucleus accumbens; R, right; RPE, reward prediction error.
[a]$p < .05$.
[b]$p < .01$.

Follow-up Data

To assess how well inflammatory responses to a laboratory stressor predicted perceived stress over the 4-month follow-up period, we examined associations between stress-induced IL-6 levels and mean PSS scores as well as mean sum of squared differences in PSS scores. The latter is a commonly used measure of symptom variability over time (62). There was no relationship between stress-induced change in IL-6 response and average PSS score over the 4-month time period. However, for participants followed for at least 1 month with available IL-6 data ($n = 47$), greater change in IL-6 following stress predicted heightened variability of perceived stress ($r = .39$, $p = .007$) (Supplemental Figure S2). We detected a similar effect for participants followed for at least 2 months ($n = 44$, $r = .37$, $p = .014$), 3 months ($n = 40$, $r = .46$, $p = .003$), and for participants completing the full 4 months of follow-up data ($n = 31$, $r = .48$, $p = .007$).

To demonstrate these relationships were not driven solely owing to the effects of mood during the MAST, multiple regression analyses were conducted to evaluate the relationship between change in IL-6 following stress and variability of perceived stress when controlling for changes in mood ratings. When controlling for VAMS rating changes, stress-induced change in IL-6 predicted perceived stress variability more strongly ($\beta = 0.60$, $t = 4.53$, $p = .00005$). As an additional control, we examined whether this association remained present when controlling for baseline PSS scores, and findings were confirmed ($\beta = -0.60$, $t = -3.54$, $p = .002$). Finally, we

additionally examined whether changes in RPE signals were similarly predictive of PSS variability, but we did not observe a significant relationship for either left ($r = -.20$, $p = .146$) or right ($r = .03$, $p = .829$) NAcc ROIs.

DISCUSSION

In this study we observed that stress-induced IL-6 was significantly predictive of subsequent stress-induced changes in NAcc RPE signals during RL. In addition, stress-induced change in IL-6 predicted variability of perceived stress in daily life over the ensuing 4 months even when controlling for stress-induced changes in mood. To our knowledge, this is the first study with a prospective component to link IL-6 and striatal RPE responses to stress, suggesting that individual differences in immune responses to stress may be a marker of vulnerability for stress-related effects on reward processes.

The relationship between cytokines and DA signaling is complex, and prior work suggests possible bidirectional pathways that may account for our observed relationships. One possibility is that acute increases in IL-6 may suppress striatal DA, thereby disrupting RPE signals (66). Evidence for such rapid (<30 minutes) effects of systemic IL-6 injections on striatal DA has been found in several rodent microdialysis studies (44,45). Moreover, such effects appear somewhat specific to striatal DA levels and have not been detected in other regions [e.g., (67)]. This interpretation is also consistent with prior work in humans showing that acute administration of cytokine inducers leads to blunted ventral striatal activity following reward cues (50), RPE signals (35), and midbrain responses to novelty (51). Similarly, chronic exposure to cytokine inducers has been shown to reduce DA availability and synthesis in primates (47,49). One caveat to this interpretation is the timing of IL-6 changes. While a statistically significant increase was observed within 30 minutes of the MAST, the magnitude of the increase was small. It is unclear whether this small increase would be sufficient to have a major effect on striatal DA. Moreover, the MIST was a less potent stressor. Consequently, it may be that the relationship is better conceptualized as a marker of individual differences in immune-striatal interactions as compared to a casual description of the direct effects of increased IL-6 on striatal function.

An alternative possibility, however, is that lower levels of DA may influence cytokine responses to stress. As noted in the introduction, DA receptors have been identified on a variety of cells within the innate immune system, including T cells and lymphocytes (52), and may regulate immune responses in the body and brain at multiple levels. Consequently, the observed relationship may be driven by the effects of stress-induced DA release on cytokine signaling. Additionally, it should be emphasized that while our analyses focused on the association between change in IL-6 and change in RPE following stress, these results should not be taken to suggest that baseline levels in either case are necessarily unrelated.

In addition to the association between inflammatory responses to stress and RPE signals, we also observed that the magnitude of IL-6 increases following stress was predictive of variability in perceived stress during a 4-month follow-up period but not of overall mean level of perceived stress. Initially, we had hypothesized that both mean and variability on PSS might be related to IL-6 responses. One explanation for this discrepancy from our hypotheses is that mean level of stress may be more determined by the presence or absence of external stressors than variability. Importantly, we found that this relationship was robust and remained significant even when controlling for sample attrition, baseline PSS scores, and stress-induced change in mood, thereby helping extend the ecological validity of our laboratory-based stress paradigms as a means to probe neurobiological responses to stress. Variability of symptom and risk factor expression is increasingly recognized as an important marker of psychological disorders (68–71), and our data suggest that variability—rather than mean level—may be a critical factor.

An important potential caveat to our findings is the lack of concurrent assessment for all measures, particularly given the absence of main effect of the MIST stressor (session 2) on striatal RPE signals or salivary cortisol. This raises the possibility that the second stress manipulation (MIST) was not as effective as the first one (MAST) and could limit the interpretability of the prestress versus poststress change in RPE signals. Specifically, it is possible that changes in RPE signals were not due to stress, given the weakness of the MIST stressor and the use of a fixed-order design, which was chosen to maximize power for individual differences analysis. Arguing against this point is the fact that there were clear increases in negative affect, and individual differences in both salivary cortisol and mood reactivity to the MAST (session 1) and MIST (session 2) stressors were correlated, suggesting that while the session 2 stressor had a less potent effect overall, the examination of individual differences across the two sessions is still valid (63).

There are several other limitations worth noting. First, our sample included female participants only. This was done to limit sex-based heterogeneity in hormonal response to stress, but it is unclear whether the current findings will extend to male subjects. While possible sex differences is a critical question, the inclusion of both genders would likely have significantly reduced our statistical power for identifying individual differences. Additionally, our study design required multiple stress sessions, which may have produced some degree of habituation. Still, we observed clear affective responses to both stressors (Figure 3), and we likely reduced habituation by using two different stress manipulations. Additionally, caution is warranted in attributing the observed changes in RL performance accuracy to the stress manipulation due to the lack of a no-stress control group for the neuroimaging session. We also note that for collection of plasma samples, we used an intravenous catheter, which may have itself stimulated some degree of IL-6 production (72). That said, this effect has generally only been observed over longer time periods (e.g., >3 hours) than were required for the current study (73). Additionally, we note that while IL-6 is generally conceptualized as being proinflammatory (43), it is important to note that it can also be anti-inflammatory depending on the target (43,74,75).

In sum, we found that stress-induced changes in IL-6 levels were associated with both striatal RPEs during RL as well as stress sensitivity during a 4-month follow-up period. These data have important implications for understanding the relationships between stress and IL-6 and their impact on reward-related corticostriatal circuitry.

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ARTICLE INFORMATION

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