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Sex differences in the relationship between inflammation and reward sensitivity: A randomized controlled trial of endotoxin

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Abstract

Background: There are robust sex differences in the prevalence of depression. Inflammation and anhedonia may play a role in understanding these sex differences. Indeed, sex differences in inflammation-induced neural responses to reward may provide insight into the sex gaps in depression, but no study has examined this question.

Methods: As such, the present study examined whether there were sex differences in reward-related neural activity (i.e., ventral striatum (VS) activity) in response to an experimental inflammatory challenge. Human participants (n=115; 69 female) were randomly assigned to receive either placebo or low-dose endotoxin, which increases inflammation in a safe, time-limited manner. Two hours after receiving placebo or endotoxin (the height of the inflammatory response to endotoxin), participants completed a task in which they anticipated monetary reward in the fMRI scanner.

Results: Results demonstrated that endotoxin (vs. placebo) led to reduced VS activity in anticipation of reward, and that there were sex differences in this effect. Specifically, in females,

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endotoxin (vs. placebo) led to decreased VS activity in anticipation of reward, but this effect was not present in males. Additionally, within the endotoxin condition, decreases in VS activity in anticipation of reward were related to increases in inflammation for females but not for males.

Conclusions: These findings may have implications for understanding how inflammation may contribute to sex differences in rates of depression.

Keywords

inflammation; reward; sex differences; anhedonia; endotoxin; depression

Introduction

It has been well-established that depression, one of the leading causes of disability worldwide (1), is more prevalent in females than males (2). Inflammation may contribute to depression in a subset of patients (3), and inflammatory processes may also play a role in the sex differences seen in depression (4). Furthermore, inflammation can induce anhedonia (5), a core symptom of depression. However, the literature thus far has been limited and inconclusive about how sex differences may play a role in the relationships between inflammation, anhedonia, and depression. To fill this gap in the literature, we examined sex differences in the impact of experimentally-induced inflammation on neural sensitivity to reward.

Mounting evidence suggests that inflammatory processes play a role in some forms of depression (3). Individuals with depression show elevated levels of pro-inflammatory cytokines (6), and experimental inflammatory challenges (e.g., endotoxin) in otherwise healthy individuals lead to elevations in depressed mood (4, 7, 8). Furthermore, treating individuals with depression who have high levels of baseline inflammation with an anti-inflammatory medication can improve depressive symptoms (9). Together, these findings suggest that inflammation is likely involved in at least some forms of depression.

Interestingly, depression is far more prevalent in females (2). While many processes likely play a role in this female preponderance of depression, there is some evidence that inflammation could be a contributing factor. For example, our group has found that females (vs. males) who are given endotoxin show greater increases in self-reported depressed mood (4). Others have also found that among patients treated with the cytokine interferon-α, which leads to a pro-inflammatory response, females are more likely than males to develop depressive symptoms (10). Thus, it is possible that females are more sensitive to the effects of inflammation on depressive symptoms.

Another potential factor that may provide insight into understanding the links between depression, inflammation, and sex is anhedonia. Anhedonia, or the loss of reactivity to pleasurable stimuli, is a core symptom of depression. At the neural level, depressed patients show dampened reactivity in the ventral striatum (VS), a reward-related neural region, in response to rewarding stimuli (11, 12). Indeed, reduced activity in the VS has been conceptualized as a neural correlate of anhedonia (5, 13–15). Furthermore, inducing inflammation via endotoxin or interferon-α can also lead to anhedonic responses, such as

reduced activation of the VS in response to the anticipation or receipt of monetary rewards; moreover, reduced VS activity is also related to self-reported depressed mood and anhedonia (5, 16). However, no prior work has examined whether there are sex differences in the effects of inflammation on VS reactivity.

While these findings point to a potential role for anhedonia in the relationship between inflammation and depression, it is indeed less clear if and how sex differences may come into play. In non-human animal models of experimental inflammation, females show more protracted anhedonic responses than males (17), and heightened inflammation suppresses sexual activity in female rats, but not male rats (18–21). While these findings suggest that females are more vulnerable to the anhedonic effects of inflammation, it should be noted that some have found equivalent inflammation-induced anhedonic responses for male and female mice (22). Furthermore, studies looking at correlations between inflammatory markers and depressive symptoms, including anhedonia, in humans have also been somewhat inconclusive. Several studies have found that correlations between inflammatory markers and depressive symptoms are stronger or only present in females (23–25), but at least one study found no evidence for a sex-specific association between inflammatory markers and anhedonia or, for some biomarkers, that males had a stronger correlation than females (26).

Thus, it appears that inflammation, depression, and anhedonia are interrelated and that there may be sex differences in these relationships, which may help explain the sex gap in depression diagnoses. However, there is an absence of studies directly examining sex differences in reward sensitivity in response to inflammation in humans. The present study helps to address this gap, and, to our knowledge, is the first study examining sex differences in the effects of experimental inflammation on neural reward sensitivity. To examine this, we randomized healthy participants to receive either endotoxin, which experimentally heightens inflammation, or placebo. At the height of the inflammatory response for endotoxin, all participants completed a monetary reward task in the fMRI scanner, where we examined reduced VS activity as a neural correlate of anhedonia. We hypothesized that females (vs. males) in the endotoxin condition would display lower VS activity to monetary reward. As a secondary hypothesis, we hypothesized that greater levels of inflammation in the endotoxin condition would be associated with lower VS activity for females but not males.

Methods and Materials

Participants and Procedures

One hundred and fifteen healthy participants (69 female; mean age: 24.2 ± 6.6 years) completed the study. Participants were deemed ineligible if they had significant physical or psychiatric issues (e.g., chronic inflammatory disorders, Axis-I psychiatric disorders), as well as if they were not deemed safe for the fMRI scan (i.e., no claustrophobia, current pregnancy, or metal implants); full exclusionary criteria are reported elsewhere (4). Sixteen participants did not have usable data for the monetary reward task (9 participants did not complete the task due to sickness symptoms, time constraints, or various other issues such as claustrophobia or previously unreported metal implants; there were technical issues with the task for 5 participants, and 2 participants did not understand the task instructions, based on a

debriefing after the task), leaving 99 participants with usable data (see Figure S2 in Supplementary Materials and Methods), with 47 participants in the control condition (27 female) and 52 participants in the endotoxin condition (33 female). Full demographic information on the sample is available elsewhere (4).

Detailed descriptions of study procedures have already been reported (4, 27), but are summarized here. None of the current data has been reported on previously; the previous paper from our group on endotoxin-induced changes in reward sensitivity reported on an entirely different sample (5). However, results previously reported from the current parent study have been published (4, 27–32). The study was conducted between March 2011 and August 2013 at the UCLA Clinical and Translational Research Center (CTRC) using a randomized, double-blind, placebo-controlled design. Ninety minutes after their arrival to the CTRC, each participant was randomly assigned to receive either low-dose endotoxin (0.8 ng/kg of body weight) or placebo (same volume of 0.9% saline), which was administered by a nurse as an intravenous bolus. The endotoxin was derived from *E. coli* (*E. coli* group O: 113: BB-IND 12948 to MRI) and provided by the National Institutes of Health Clinical Center (33). Of the 115 participants, 54 were randomized into the placebo condition and 61 were randomized into the endotoxin condition.

Approximately two hours after receiving either the endotoxin or placebo injection (when the inflammatory response peaks for the endotoxin condition; 4, 7, 27), participants were scanned as they completed the monetary reward task (see below for more detail) in the fMRI scanner. Hourly blood draws were taken throughout the session to assess levels of pro-inflammatory cytokines (at baseline prior to endotoxin/placebo administration and then approximately every hour over a total time of six and a half hours after endotoxin/placebo administration). Cytokine analyses for the current study focus on the baseline time point and the pre-scan time point (approximately 2 hours post-injection) because the second time point was closest to when the fMRI data were collected.

All subjects provided written consent before participating. All procedures were approved by the UCLA Human Subjects Protection Committee. The study was registered as a Clinical Trial (#NCT01671150).

fMRI Imaging Paradigm

To assess neural responses to reward anticipation, participants were scanned while completing the monetary incentive delay (MID) task (5, 34). While still at the CTRC, participants were given instructions for the MID task. Participants were told that on each trial, they would see a cue indicating how much money they could win or lose on that trial and that, following this cue, they would see a target. On trials in which the cue indicated a potential win, participants could win money if they pressed a button during a briefly-presented target presentation. Alternatively, on trials in which the cue indicated a potential loss, participants could avoid losing money if they pressed a button during the target presentation. During the neutral trials, participants' earnings would not change, but they were still instructed to press the button as quickly as possible following the cue. After receiving the instructions, participants completed a practice version of the task to produce an estimate of each participant's reaction time for standardizing task difficulty in the scanner.

During the MID task, participants saw 65 6-second trials. During each trial, participants saw one of five cue shapes (cue, 250 msec) that indicated how much money they could win or avoid losing, followed by a crosshair as they waited a variable interval (delay, 2000–2500 msec), and then a white target square that appeared for a variable length of time (target, 166–333 msec). If participants could press a button while the target was on the screen, they won money, avoided losing money, or stayed even (depending on the type of cue). Feedback information (feedback, 1753 msec) followed the target and notified participants about their earnings on the previous trial, as well as their cumulative earnings at that point. Task difficulty, based on reaction times collected during the practice session, was set such that participants would succeed on approximately 66% of their target responses. Cues signaled potential reward (circles), potential loss (squares), or no monetary outcome (triangles). The number of horizontal lines in the cues indicated the magnitude of the possible reward (+ $1.00: n = 13, one horizontal line; + $3.00; n = 13, three horizontal lines) or loss (− $1.00: n = 13, one horizontal line; − $3.00: n = 13, three horizontal lines). Trial types were pseudorandomly ordered within the scanning session. A sample trial from the MID task is included in Figure 1.

fMRI Acquisition and Preprocessing

Imaging data were acquired on a Siemens 3 T “Tim Trio” MRI scanner housed at UCLA’s Staglin IMHRO Center for Cognitive Neuroscience. Foam padding was placed around the participants’ head for comfort and to constrain head movement. A T2-weighted, matched-bandwidth anatomical scan (slice thickness = 3 mm, gap = 1 mm, 36 slices, TR = 5000 ms, TE = 34 ms, flip angle = 90°, matrix size 128 × 128, FOV = 200 mm) was acquired for each participant, followed by a functional scan lasting approximately 9 minutes (echo planar T2-weighted gradient echo, TR = 2000 ms, TE = 25 ms, flip angle = 90°, matrix size 64 × 64, 36 axial slices, FOV = 200 mm; 3-mm thick, skip 1-mm).

fMRI data were preprocessed via SPM12 (Wellcome Department of Imaging Neuroscience, London) using the DARTEL (Diffeomorphic Anatomical Registration Through Exponential Lie Algebra) pipeline. For each subject, functional images were realigned and resliced to the mean functional image to correct for head motion. Afterwards, the matched-bandwidth (MBW) anatomical scan was coregistered to the mean functional image then segmented. The resulting MBW images and segmentation parameters were used to create a group-specific image template, which was affine-registered into Montreal Neurological Institute (MNI) space. Deformation fields generated in the previous step were used to normalize all images into MNI space, with functional images undergoing integrated spatial smoothing (8 mm, Gaussian kernel, full-width at half-maximum).

Plasma Levels of Cytokines

Whole blood samples were collected in pre-chilled EDTA tubes. After collection, the samples were centrifuged at 4°C, plasma was harvested into multiple aliquots, and then stored in a −70°C freezer until the completion of the study.

Plasma tumor necrosis factor (TNF)-α and interleukin (IL)-6 concentrations (assay ranges 0.8–3100 pg/mL and 0.2–3800 pg/mL, respectively) were determined using a Bio-Plex 200

(Luminex) Instrument, and a high sensitivity bead-based multiplex immunoassay (Performance High Sensitivity Human Cytokine, R& D Systems, Minneapolis, MN), as previously described (4, 27, 31). The full cytokine profile for participants from this exact study are available in other publications (4, 27). All plasma samples from each subject (baseline and all subsequent time points) were assayed on the same 96-well plate; every subject demonstrated the expected profile of cytokine concentrations over time, based on previous studies (7, 35). The mean intra-assay CV% of the standards was < 8% for TNF-α and IL-6; the inter-assay CV% of an internal laboratory quality control sample was < 13% for both analytes.

Statistical Analyses

Cytokine data—Full details of the overall effects of endotoxin on cytokine levels are reported elsewhere (4, 27). For the between-condition and correlational analyses in the present study, we focused on the baseline timepoint (prior to injection; *T0*) and the timepoint immediately preceding the fMRI scan (approximately 2 hours post-injection; *T2*). All cytokine data were natural log-transformed to correct for skew prior to analysis, and because of known effects of body mass index (BMI) on cytokines, we controlled for BMI in all cytokine analyses.

Behavioral data from MID task—We examined differences between conditions (endotoxin vs. placebo) and condition*sex interactions in hit rates (successful button presses during target presentation) to reward trials, reaction times to reward trials, and total monetary earnings across the task. Between-condition differences were tested using independent sample t-tests and condition*sex interactions were tested using ANOVAs.

fMRI data—Single-subject whole-brain analyses were conducted using SPM12. To estimate hemodynamic (BOLD) responses, the general linear model was used to model the following events within each subject: the anticipation period for each cue type, which began with the presentation of the cue (i.e., +$1.00, $3.00 for reward; −$1.00, −$3.00 for loss; $0.00 for neutral) and the feedback period after successful (hit) and unsuccessful (miss) target responses. Motion parameters from the realignment step were used as nuisance regressors to dampen the impact of remaining motion artifacts. Each model was convolved with the canonical double-gamma hemodynamic response function, and was high-pass filtered at 1/128 Hz. Analyses focused on reward anticipation, as the anticipation of reward most robustly activates the VS (34). Within each subject, the reward, loss, and neutral anticipation periods were contrasted with the implicit baseline; parameter estimates from these three contrasts were used for all further fMRI analysis.

Given our a priori hypotheses regarding inflammation-induced reductions in reward-related neural responding, we conducted region of interest (ROI) analyses focusing on activity within the left and right VS. The VS ROI was structurally defined by combining the left and right caudate and putamen from the Automated Anatomical Labeling Atlas (36) of the Wakeforest University Pickatlas (37) and then constraining the regions to $-24 < x < 24$, $4 < y < 18$,$-12 < z < 0$ based on coordinates showing increased VS activity to the anticipation of reward in prior studies (38, 39). ROI parameter estimates were derived by averaging the

values of all voxels within an ROI for each contrast and subject. ROI parameter estimates (left VS, right VS, and bilateral VS) were used to investigate the relationships between neural responses and condition (endotoxin, placebo), sex (male, female), and cytokine levels. ROIs are reported bilaterally (averaged across left and right ROIs), as laterality was not of interest in the present study. Based on convention, all analyses involving imaging data were one-tailed.

Results

Inflammatory Responses

As reported previously (4, 27, 31), endotoxin led to significant increases in circulating levels of IL-6 and TNF-α at *T2*, controlling for BMI and *T0* values (p's < .001), but there were no sex differences in the cytokine responses (p's > .8).

Behavioral Responses to MID Task

There were no significant condition differences (endotoxin vs. placebo) or condition*sex interactions in hit rates (successful button presses during target presentation) to reward trials (p's > .1) or in reaction times to reward trials (p's > .2). There were also no between-condition differences or condition*sex interactions in total monetary earnings across the task (p's > .1). Thus, any between-condition or sex differences in neural responding to reward trials should reflect differences in neural sensitivity to reward anticipation and not differences in rewarding outcomes to the task.

Neural Responses to the MID Task

Based on prior findings (5), we first examined whether endotoxin (vs. placebo) led to lower activity in the VS to the anticipation of reward. Consistent with our prior work (5), subjects exposed to endotoxin, vs. placebo, showed less activity in the bilateral VS in anticipation of reward trials (p < .05; Figure 2). We then examined whether there were sex differences in these effects to test our primary hypothesis.

As hypothesized, there were condition by sex interactions for the bilateral VS ($F(1,95)=2.95$, p = .089; Figure 3). Follow-up analyses showed that females showed significantly less VS activity in the endotoxin condition than the placebo condition (Bilateral VS: $t(58)=2.46$; p < .01) but males did not (p > .4).

Correlations Between VS Activity During Anticipation of Reward and Cytokines

To better understand the sex differences in the inflammation-induced decreases in VS responses, we also examined correlations between VS activity in the anticipation of reward and cytokine levels at *T2*, controlling for *T0* values and BMI. We first examined associations collapsed across sexes, and then females and males separately, for subjects within the endotoxin condition.

Within the full endotoxin sample (across both sexes), there were significant negative correlations between bilateral VS activity and IL-6 ($r = -.42$; p < .01), as well as between bilateral VS and TNF-α ($r = -.26$; p < .05).

When examining males and females separately, correlations between VS activity and cytokines were significant for females but not for males, such that higher levels of cytokines were associated with lower VS activity for females but not for males. This was true for IL-6 and bilateral VS activity (Figure 4A and 4B; females: $r = -.50$, $p = < .01$; males: $r = -.20$, $p = .23$). These same effects (significant correlations between higher cytokine levels and lower VS activity females, but not males) were also found for TNF-α and bilateral VS activity (Figure 4C and 4D; females: $r = -.36$, $p < .05$; males: $r = -.10$; $p = .36$).

Discussion

Females are two to three times more likely than males to develop depression but it remains unclear why (2, 40–42). Previous findings in the literature have suggested that inflammation-induced anhedonia may play an important role in understanding these sex differences. However, no studies have directly examined sex differences in neural sensitivity to reward in response to an experimental inflammatory challenge. Such sex differences in inflammation-induced responses to reward may ultimately help explain sex differences in rates of depression. Thus, in the present study, we sought to address this gap in the literature by examining whether there were sex differences in VS responses to reward after an experimental inflammatory challenge.

To our knowledge, this is the first study to establish sex differences in neural sensitivity to reward in response to inflammation. As hypothesized, there were sex differences in the effect of endotoxin on neural sensitivity to reward. Indeed, females in the endotoxin condition showed less VS activity (vs. females in the placebo condition) during anticipation of reward, but this condition effect was not present in males. The VS responsiveness in the females in the placebo group may appear to stand out more than the response in the endotoxin group (see Figure 3). However, this is informative; with the placebo group acting as a control or baseline condition, the lower VS response in the females in the endotoxin group suggests that endotoxin led to reduced VS activity in females compared to what would one would expect under basal or control conditions. Although novel on their own, these findings build on and extend findings in the literature. Work in non-human animals has found that females have a more protracted anhedonic response to inflammation (17), and correlations between markers of inflammation and depressive symptoms in humans are often stronger or only present in females (23–25). Together with previous findings, our results suggest that inflammatory-induced anhedonia, as indexed by reduced VS activity, may contribute to the well-established sex differences found in rates of depression.

Furthermore, within the endotoxin condition, increases in pro-inflammatory cytokines were related to reduced VS activity in response to anticipation of reward for females, but not for males. These findings complement findings in the literature suggesting that women with chronic inflammatory disorders (e.g., arthritis, multiple sclerosis) are at an increased risk for developing depression (43–45). The sex-specific correlation between levels of inflammation and reward sensitivity in our findings suggest that these women may be especially vulnerable to depression specifically via decreases in reward sensitivity. These findings suggest that clinicians may want to more carefully examine symptoms of anhedonia in women with high levels of inflammation.

This study was not without limitations. First, the sample was young and healthy. As such, neural sensitivity to reward in response to inflammation may look different in an older sample. However, this young sample (vs. an older sample) was appropriate for studying potential contributors to sex differences in depression, as sex differences in the prevalence of depression are not typically found in older samples (46). Additionally, the findings may not extend to a clinical sample (e.g., patients with major depression or other chronic health issues). Indeed, the brain's response to reward in the context of chronic inflammation may vary from the acute inflammatory response studied here. In addition, the reward task used in this study involved money and was inherently non-social. Our group has found that neural sensitivity to reward in response to inflammation varies between non-social and social forms of reward (7, 30, 32, 47). Thus, the findings in this study may not extend to other forms of reward, particularly those that are social in nature.

Overall, this study highlights the need to further examine and understand the mechanisms behind the sex differences commonly reported in the depression literature. In the present study, we found that there were sex differences in anhedonia, as indexed by neural sensitivity to reward anticipation, in response to an experimental inflammatory challenge. Indeed, females displayed a greater inflammatory-induced anhedonic response. This finding suggests that reduced VS activity in response to inflammation may play an important role in understanding why females experience depression at rates far higher than males. Furthermore, given the correlations between heightened inflammatory markers and reduced VS activity in females, females with higher levels of inflammation, such as those with chronic inflammatory disorders, may be at particular risk for depression via decreases in reward sensitivity. Future work is needed to replicate and extend these findings to more fully elucidate the links between sex, inflammation, and anhedonia, and how these relationships may be used to understand sex differences in depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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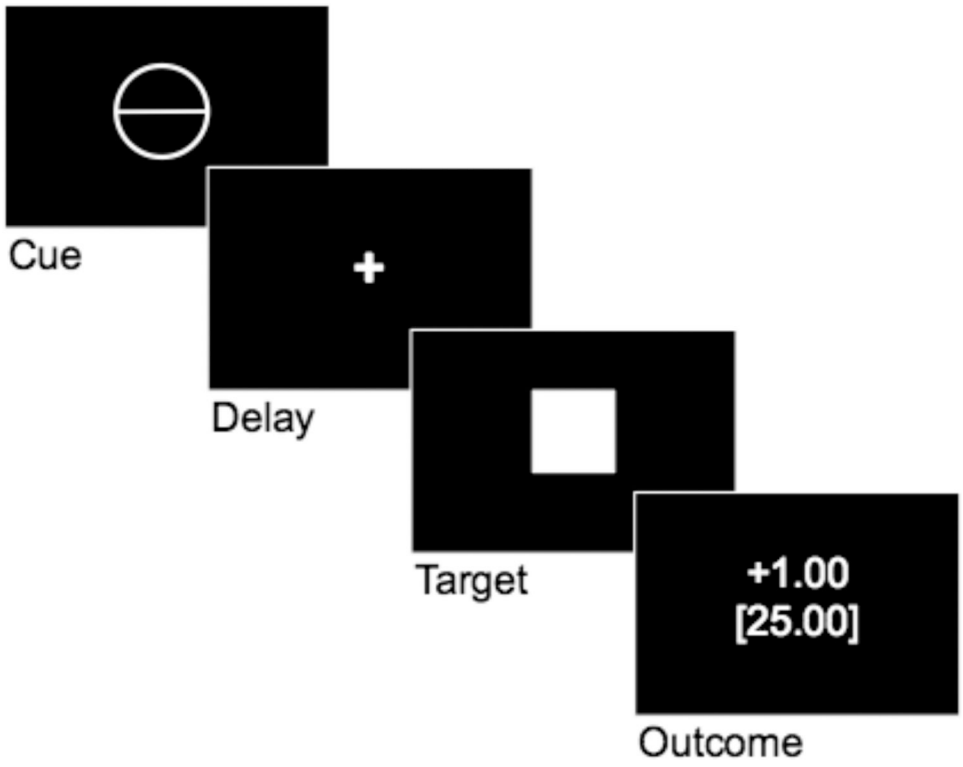

Figure 1.
A sample trial from the monetary incentive delay (MID) task.

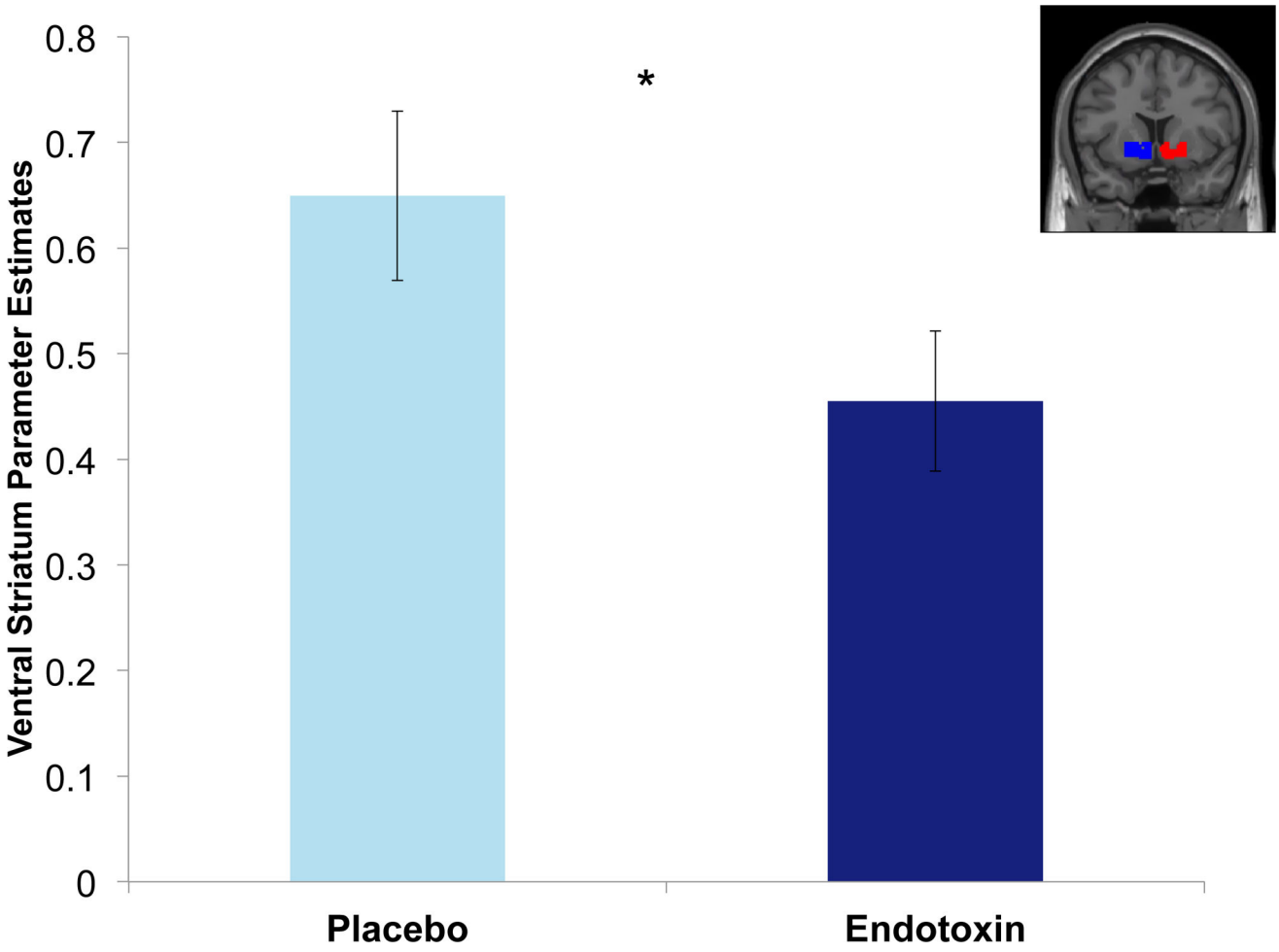

Figure 2.

Neural activity (mean parameter estimates) in response to the anticipation of reward for bilateral ventral striatum regions of interest as a function of condition (endotoxin vs. placebo). One asterisk denotes $p < .05$.

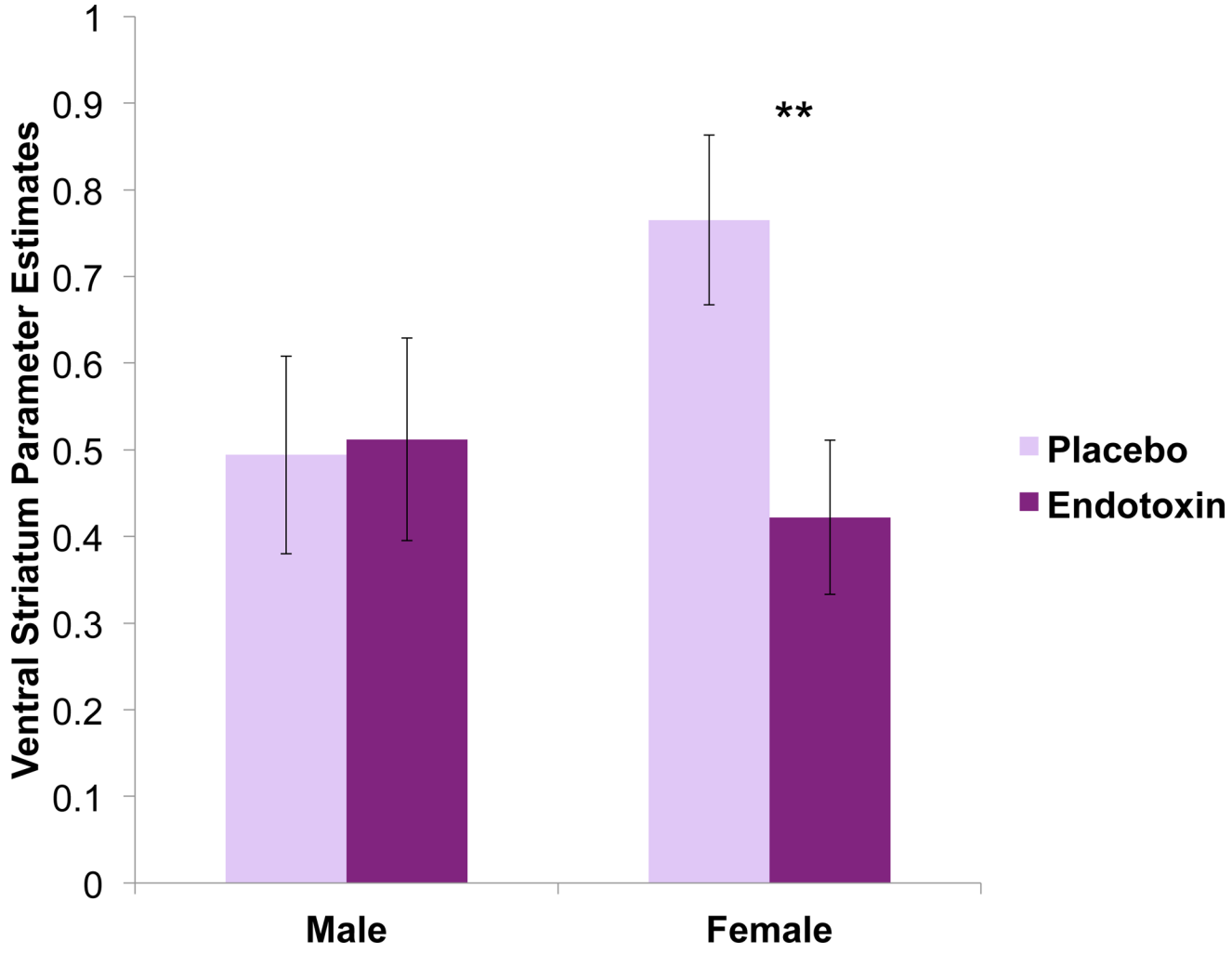

Figure 3.

Neural activity (mean parameter estimates for bilateral ventral striatum regions of interest) in response to the anticipation of reward as a function of condition (endotoxin vs. placebo) and sex. Two asterisks denotes $p < .01$.

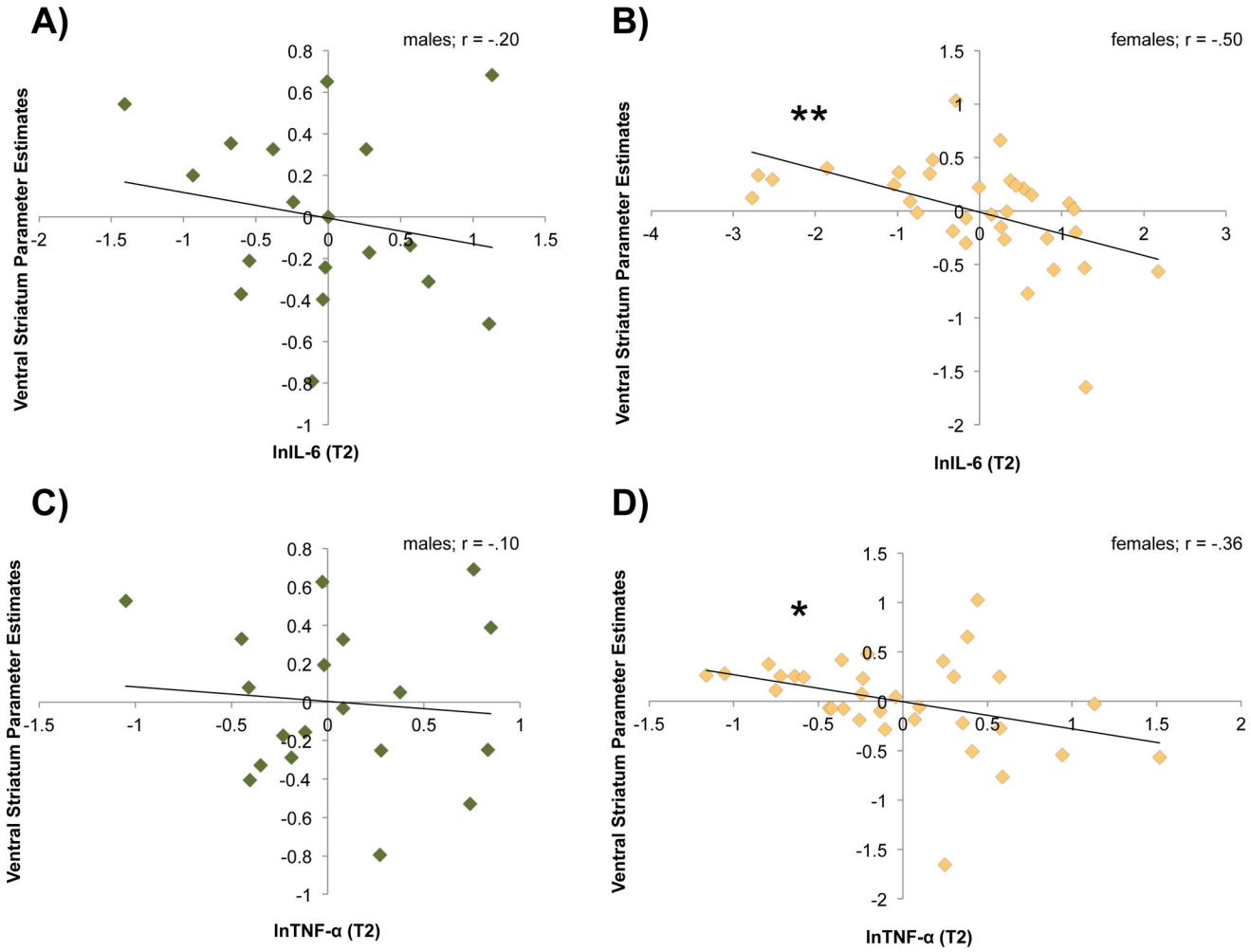

Figure 4.

Correlations between cytokines and neural activity (mean parameter estimates for bilateral ventral striatum (VS) regions of interest) in response to anticipation of reward. Correlations between VS activity and levels of IL-6 at *T2* shown separately for a) males and b) females, as well as VS activity and levels of TNF-α at *T2* shown separately for c) males and d) females. All displayed values and statistical analyses controlled for body mass index (BMI) and *T0* values of cytokines. One asterisk denotes $p < .05$, and two asterisks denotes $p < .01$.