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# The role of the ventral striatum in inflammatory-induced approach toward support figures

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ABSTRACT

Although considerable research has shown that inflammation leads to social withdrawal more generally, it is also possible that inflammation leads to social approach when it comes to close others. Whereas it may be adaptive to withdraw from strangers when sick, it may be beneficial to seek out close others for assistance, protection, or care when sick. However, this possibility has never been explored in humans nor have the neural substrates of these behavioral changes. Based on the role of the ventral striatum (VS) in responding to: (1) the anticipation of and motivation to approach rewarding outcomes and (2) viewing social support figures, the VS may also be involved in sickness-induced approach toward support figures. Thus, the goal of the present study was to examine whether inflammation leads to a greater desire to approach support figures and greater VS activity to viewing support figures. To examine this, 63 participants received either placebo or low-dose endotoxin, which safely triggers an inflammatory response. Participants reported how much they desired to be around a self-identified support figure, and viewed pictures of that support figure while undergoing an fMRI scan to assess reward-related neural activity. In line with hypotheses, endotoxin (vs. placebo) led participants to report a greater desire to be around their support figure. In addition, endotoxin (vs. placebo) led to greater VS activity to images of support figures (vs. strangers), and greater increases in inflammation (IL-6 levels) were associated with greater increases in VS activity. Together, these results reveal a possible neural mechanism important for sickness-induced social approach and highlight the need for a more nuanced view of changes in social behavior during sickness.



## 1. Introduction

As part of the innate immune response, an organism will exhibit a multitude of symptoms, termed "sickness behavior," in response to infection or illness. Symptoms of sickness are triggered by the release of proinflammatory cytokines, which act as chemical messengers to signal the brain to change behavior. The most commonly observed inflammatory-induced change in social behavior has been withdrawal from others. Thus, animal research has shown that an acute inflammatory challenge leads to reduced social exploration of others (Bluthe et al., 1996, 1994; Marvel et al., 2004). Similarly, humans exposed to an experimental inflammatory challenge report increased feelings of social disconnection (Eisenberger et al., 2010) and greater threat-related neural activity to negatively-valenced pictures of unknown others (Inagaki et al., 2012). Though unpleasant in the short-term, changes in social behavior such as social withdrawal are thought to be adaptive responses in promoting rest and recuperation from illness or infection (Dantzer et al., 2008; Hart, 1988).

Despite this literature linking inflammation and social withdrawal, animal models have shown that, under certain circumstances, animals will engage in more rather than less social behavior during sickness (Aubert, 1999; Hennessy et al., 2014). This is particularly true when given the chance to affiliate with a familiar other. For instance, after being injected with lipopolysaccharide (LPS), which elicits an inflammatory response, rats spend more time huddling with familiar cage-mates as compared to responses of placebo-injected controls (Yee and Prendergast, 2010). Increases in

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affiliative social behavior during sickness have also been observed in non-human primates. At a relatively low dose, LPS-treated rhesus monkeys (vs. saline-treated control monkeys) show significantly more close social contact with cage-mates and, at the higher dose, proximal social contact (defined as passively sitting near a companion) is positively correlated with levels of interleukin-6 (IL-6), an inflammatory cytokine and well-known mediator of sickness behavior (Dantzer, 2001; Willette et al., 2007). Thus, depending on the target of the social behavior, sickness can lead to increased approach toward others.

In fact, increasing interactions with close, supportive individuals may confer a survival advantage should those close individuals provide care and protection to the sick (Cole, 2006; Hennessy et al., 2014). In other words, just as it may be important to withdraw from strangers or signs of threat during sickness, it may be just as important to approach close others in order to obtain care. Indeed, sickness increases social approach behavior toward close others in young children, such that infants or children who are sick become more clingy, spend more time in proximity with their caregivers, and become more upset following separation from their caregivers (Ainsworth, 1973; Bowlby, 1988; Mikulincer and Shaver, 2007). However, the effect of inflammation on the motivation to approach support figures has not yet been explored in humans.

In addition, the neural regions underlying motivations to approach loved ones during times of sickness are currently unknown. Results from studies of the neurobiology of close social relationships suggest that regions related to reward processing, especially the ventral striatum (VS), underlie feelings of social connection in close relationships (Aron et al., 2005; Acevedo et al., 2012; Inagaki and Eisenberger, 2013). For instance, reminders of close others in the neuroimaging environment, such as loving messages from close others (Inagaki and Eisenberger, 2013) or pictures of a loved one (Acevedo et al., 2012; Strathearn et al., 2009, 2008) robustly activate the VS. In addition, the VS is particularly sensitive to the motivation to approach highly pleasing rewards such as money or sweet tastes (Berridge et al., 2009; Knutson and Cooper, 2005). Thus it appears as if the VS is sensitive both to the motivation to approach rewards as well as close support figures and therefore may be associated with social approach during sickness as well.

The current study assessed the effect of an experimentally induced inflammatory challenge on the motivation to approach a support figure. Based on results from the animal literature, we expected inflammation (vs. placebo) to lead to a greater self-reported desire to be around support figures. We also investigated whether inflammation altered neural activity in a key reward-related brain region in response to viewing photographs of a social support figure, but not to photographs of an unknown stranger. We hypothesized that individuals exposed to an inflammatory challenge (vs. a placebo) would show greater neural activity in the VS in response to viewing pictures of their support figure, but would show no differences in response to viewing pictures of a stranger. Finally, we explored the association between endotoxin-induced changes in the proinflammatory cytokines, IL-6 and TNF-α, and VS activity to viewing support figures with the hypothesis that increases in cytokines would be associated with greater VS activity.

## 2. Methods

### 2.1. Overview

Detailed descriptions of similar methods have been published elsewhere (Eisenberger et al., 2010, 2009; Inagaki et al., 2012), but are summarized here. Participants were deemed eligible to participate after being evaluated for psychiatric conditions (via the Structure Clinical Interview for DSM Axis I Disorders; First et al., 2012), scanner-safety (claustrophobia and for the females, pregnancy), and general health (vitals, BMI, blood draw). Following screening, eligible participants were contacted and asked to send digital photographs of a self-identified support figure for the scanner task. On the day of the experimental session, participants were randomly assigned to receive low dose endotoxin, which safely triggers an inflammatory response, or placebo. Approximately 2 h after injection, when the inflammatory response begins to peak (Eisenberger et al., 2009, 2010), all participants were asked about their desire to be around their support figure and then underwent an fMRI scan where they viewed images of their support figure and a sex, race, age and expression matched stranger (see below for more details). Hourly blood draws were taken throughout the experimental protocol to assess levels of inflammation (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 focused on the baseline time point and the post-scan time point because this second time point was closest to when the fMRI task was collected and because our prior work has shown sustained increases in cytokines (relative to baseline) at this time (Eisenberger et al., 2009, 2010).

### 2.2. Participants

115 participants (69 females, *M age* = 24.17, *SD* = 6.61) were randomly assigned to receive low dose endotoxin (0.8 ng/kg of body weight, O: 113; *n* = 61) or placebo (0.9% saline; *n* = 54) administered as an IV bolus over a 30–60 s period through a catheter placed in the non-dominant forearm. Of this sample, 52 participants were not run through the support figure task due to logistical constraints (i.e. some participants failed to respond to email requests for pictures of a support figure, last minute scheduling changes did not allow sufficient time to collect pictures, the reserved scanning time would end before we were able to acquire data for this task). These constraints left a sample of 63 participants (*M age* = 24.25, *SD* = 6.56, *n endotoxin* = 32 (18 females), *n placebo* = 31 (16 females)) who completed the support figure task. The ethnic breakdown of this sample was as follows: 39.7% Caucasian, 33.3%, Asian/Pacific Islander, 17.5% Latino, 6.3% Other, and 3.2% African American. All procedures were run in accordance with UCLA's Institutional Review Board.

### 2.3. Pre-session ratings

Prior to the experimental session, eligible participants were emailed and asked to send the experimenters two digital photographs of a support figure. Specifically they were instructed to send pictures of someone they could go to for help or for comfort (for example, a family member, a close friend, or a significant other). Additionally, participants rated whether they could "really count on this person to help them feel better when they are feeling generally down-in-the-dumps" and how much they can "rely on this person for help if they have a serious problem" on a 1–7 scale, with 1 corresponding to "not at all" and 7 corresponding to "a lot". Overall ratings on these two measures were high (*M* = 6.46, *SD* = .84 for "really count on this person" and *M* = 6.52, *SD* = .95 for "rely on this person"), indicating that they were in fact support figures. No differences in these ratings were found between those in the endotoxin condition and those in the placebo condition (*p's* > .55).