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Commentary

Context-Dependent Effects of Inflammation: Reduced Reward Responding is Not an Invariant Outcome of Sickness

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The inflammatory response of the innate immune system is thought to contribute to the pathophysiology of some types of depression. Depression is associated with elevated levels of markers of systemic inflammation (eg, C-reactive protein) as well as inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α. In addition, both C-reactive protein and inflammatory cytokines are reported to correlate prospectively with the onset of major depressive disorder (Slavich and Irwin, 2014). Increasingly, experimental paradigms have been used to evaluate the causal role of inflammation on depressive symptoms, given evidence that acute inflammatory reactivity to laboratory-based challenges is clinically meaningful in predicting increases in depression over the following year (Slavich and Irwin, 2014). Indeed, one model of experimentally induced inflammation, endotoxin administration, can serve as a potent approach to interrogate the role of inflammation on depressive symptom induction, and to identify the neurobiological substrates that subserve these clinical changes (Schedlowski *et al*, 2014).

Endotoxin administration induces two cardinal affective symptoms, depressed mood and anhedonia, which are key elements of depression (Schedlowski *et al*, 2014). Whereas the current diagnostic criterion of anhedonia can be met through demonstrated 'loss of interest or pleasure', the 'wanting' and 'liking' aspects of anhedonia may represent different components of reward behavior. In this study, Lasselin *et al* (2016) addressed this question, examined how inflammation influences anhedonia, and tested whether inflammation and associated subjective states such as sleepiness alter motivation, sensitivity to monetary reward, or both (Lasselin *et al*, 2016). In so doing, the findings of Lasselin *et al* (2016) challenge a widely accepted view that inflammation reduces incentive motivation or the willingness to expend effort to obtain a reward (Lasselin *et al*, 2016) and further suggest that diagnostic 'lumping' of interest and pleasure may be out of step with neurobiological reality (Felger and Treadway, 2016).

In animals, inflammation induces changes in motivational behavior that are characterized by a reduction in incentive motivation, as well as sensitivity to reward (Eisenberger *et al*, 2016). Likewise in human, inflammation reduces reward-related neural responding to monetary rewards, but whether this response is driven by incentive motivation or sensitivity to reward is not yet clear (Eisenberger *et al*, 2016). However, Lasselin *et al* (2016) found that endotoxin alters motivational behaviors in ways which are much more nuanced, in which responses seem to be aligned with the nature of the task (ie, level of demand and level of reward), probability of receiving reward, and subjective state (ie, sleepiness) (Lasselin *et al*, 2016). For example, when the probability to win monetary reward is the highest, humans choose high effort and high reward modes of response, and this choice is even more pronounced after exposure to inflammatory challenge. Moreover, these motivational changes appear to be related, and possibly mediated, by increases in sleepiness that are known to be induced by increases in inflammation. In other words, when effort is deemed worthwhile, humans, who are exposed to inflammation and show increased levels of sleepiness, reorganize their priorities and are more discerning or finicky in their effort allocation.

Inflammation has also been shown to have a powerful influence on social processes (Eisenberger *et al*, 2016), and might serve as a transduction signal linking social processes and depression (Slavich and Irwin, 2014). Thus, a critical extension of the findings of Lasselin *et al* (2016), which focused on monetary reward, is whether inflammation alters the 'wanting' and 'likings' aspects of social rewards (Lasselin *et al*, 2016). Further, if inflammation is found to increase motivation for certain types of social bonds characterized by higher level of reward (ie, affiliative contact with close others) as suggested (Eisenberger *et al*, 2016), and this response is preserved or even amplified in inflammatory-related depression, therapeutic interventions could be refined that better incorporate care from close others. Such tailored interventions that take into account social reward processes may improve the efficacy of antidepressant medications;

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depressed patients with high levels of inflammation show an attenuated response to antidepressants. Alternatively, given that dopaminergic systems subserve reward-related behaviors, and that inflammation affects multiple aspects of dopamine transmission, this experimental research could also inform understanding of the neurobiological mechanisms linking inflammation and depression, with the potential to guide development of novel therapies that target dopamine relevant behavioral sensitivities to improve depression treatments (Felger and Treadway, 2016).

It is not known whether the results of Lasselin *et al* (2016) are generalizable to social reward (Lasselin *et al*, 2016). Nevertheless, inflammation appears to induce a heightened sensitivity to both positive and negative social stimuli, which may help an individual discern and prioritize who should be avoided and who might be supportive in providing help (Eisenberger *et al*, 2016). For example, endotoxin administration has been found to increase sensitivity to threatening social, but not threatening, non-social, stimuli, which possibly triggers withdrawal from unfriendly others (Eisenberger *et al*, 2016). In contrast, when humans are exposed to endotoxin and view images of loved ones, but not strangers, there is greater neural activity in the ventral striatum, a key reward-related neural region, and this response correlates with greater increases in circulating markers of inflammation (ie, interleukin-6) (Eisenberger *et al*, 2016). Further, such experimental increases in inflammation alter how a person responds to positive social feedback, with evidence of more reward-related activity in the ventral striatum as well as in the ventromedial prefrontal cortex, another reward-related brain site (Eisenberger *et al*, 2016). Although incentive motivation was not evaluated, inflammation appears to heighten an individual's social discernment of who might be an ally during times of increased vulnerability, and possibly during episodes of depression.

Although not examined by Lasselin *et al* (2016), biological variability, and especially sex differences, may play a critical role in behavioral responses to inflammatory challenge. For example, Moieni *et al* (2015) found that endotoxin induced greater increases in depressed mood and feelings of social disconnection in females, as compared with males, and these differences were due to an increased behavioral sensitivity to inflammatory cytokines in females (Moieni *et al*, 2015). Moreover, the presence of pre-existing sleep disturbance leads to a heightened depression response to endotoxin, especially in females, which together suggest that inflammation and sleep disturbance (or sleepiness, as noted by Lasselin *et al*, 2016) serve as 'two hits' to alter incentive motivation and reward sensitivity, and the reorganization of demand priorities (Cho *et al*, 2016; Irwin and Opp, 2016). To the extent that female sex and sleep disturbance are potent risk factors for depression, understanding how inflammatory challenge differentially triggers depression in association with these 'hits' of vulnerability might accelerate development of precision-based strategies to monitor high-risk populations to prevent depression when exposed to heightened states of inflammation such as infections and interpersonal stress.

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