www.neuropsychopharmacology.org

Commentary

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

Michael R Irwin*,1,2,3 and Naomi I Eisenberger³

¹Cousins Center for Psychoneuroimmunology, UCLA Semel Institute for Neuroscience, Los Angeles, CA, USA; ²Department of Psychiatry and Biobehavioral Sciences, UCLA David Geffen School of Medicine, Los Angeles, CA, USA; ³Department of Psychology, UCLA, Los Angeles, CA, USA

Neuropsychopharmacology (2017) 42, 785-786; doi:10.1038/npp.2016.245; published online 16 November 2016

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

*Correspondence: Professor MR Irwin, Department of Psychiatry and Biobehavioral Sciences, UCLA David Geffen School of Medicine, Los Angeles, CA 90095, USA. E-mail: michaelirwin1@mac.com Received 30 September 2016; revised 4 October 2016; accepted 7 October 2016; accepted article preview online 25 October 2016 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 rewardrelated 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 inflammatoryrelated 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; 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 highrisk populations to prevent depression when exposed to heightened states of inflammation such as infections and interpersonal stress.

FUNDING AND DISCLOSURE

This research was funded by the following from NIH to MRI (R01-AG034588, R01AG026364, R01CA160245-01, R01CA119159, R01HL095799 and R01DA032922) and from NIMH to NIE (5R01MH091352). The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We acknowledge the Cousins Center for Psychoneuroimmunology at the UCLA Semel Institute.

REFERENCES

Cho HJ, Eisenberger NI, Olmstead R, Breen EC, Irwin MR (2016). Preexisting mild sleep disturbance as a vulnerability factor for inflammation-induced depressed mood: a human experimental study. *Transl Psychiatry* 6: e750.

Eisenberger NI, Moieni M, Inagaki TK, Muscatell KA, Irwin MR (2016). In sickness and in health: the co-regulation of inflammation and social behavior. *Neuropsychopharmacology* (e-pub ahead of print).

Felger JC, Treadway MT (2016). Inflammation effects on motivation and motor activity: role of dopamine. *Neuropsychopharmacology* (e-pub ahead of print).

Irwin MR, Opp MR (2016). Sleep health: reciprocal regulation of sleep and innate immunity. *Neuropsychopharmacology* (e-pub ahead of print).

Lasselin J, Treadway MT, Lacourt TE, Soop A, Olsson MJ, Karshikoff B *et al* (2016). Lipopolysaccharide alters motivated behavior in a monetary reward task: a randomized trial. *Neuropsychopharmacology* (e-pub ahead of print).

Moieni M, Irwin MR, Jevtic I, Olmstead R, Breen EC, Eisenberger NI (2015). Sex differences in depressive and socioemotional responses to an inflammatory challenge: implications for sex differences in depression. *Neuropsychopharmacology* **40**: 1709–1716.

Schedlowski M, Engler H, Grigoleit JS (2014). Endotoxin-induced experimental systemic inflammation in humans: a model to disentangle immune-to-brain communication. *Brain Behav Immun* 35: 1–8.

Slavich GM, Irwin MR (2014). From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychol Bull* 140: 774–815.