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Mandakh Bekhbat, *Emory University*
[Gretchen Neigh](#), *Emory University*

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Stress-induced neuroimmune priming in males and females: comparable but not identical

Mandakh Bekhbat¹ and Gretchen N. Neigh^{1,2,*}

¹Neuroscience Graduate Studies Program, Emory University, Atlanta, GA

²Department of Anatomy & Neurobiology, Virginia Commonwealth University, Richmond, VA

Chronic stress is a reliable predictor of several psychiatric illnesses including major depressive disorder, and anxiety disorders which are more prevalent in women compared to men. Extensive evidence from human and rodent studies demonstrates that a history of stress promotes pro-inflammatory outcomes in the brain and the body, and can lead to immune priming – a sensitized response to a subthreshold or secondary challenge. However, it is currently unclear whether the female bias in depressive and anxiety disorders is fueled by sex differences in the extent to which stress sensitizes immune processes (Bekhbat and Neigh, 2018).

To date, studies conducted in male rodents have demonstrated that prior stress can prime central expression of pro-inflammatory cytokines (Audet et al., 2011), pro-inflammatory transcription factor activity (Munhoz et al., 2006), microglial activation (Frank et al., 2007), and immune cell trafficking to the brain (Wohleb et al., 2013). In this issue of *Brain, Behavior, and Immunity*, Fonken et al. (2018) investigate sex differences in sickness behavior, hippocampal and peripheral cytokine expression, and microglial activation *ex vivo* using an inescapable tail shock stress model in male and female rats. Twenty-four hours following inescapable tail shock stress male and female rats were challenged with a systemic injection of lipopolysaccharide (LPS), or in *ex vivo* experiments, hippocampal microglia were isolated and stimulated with LPS in culture. The central question addressed by Fonken et al. (2018) is “Do females display stress-induced neuroimmune priming?” The authors demonstrate that comparable to stressed males, stressed females indeed display exaggerated sickness behavior that was accompanied by primed hippocampal pro-inflammatory cytokine expression and reduced expression of anti-inflammatory signaling molecules including CD200R and CX3CR1 when assessed 24 hours after shock exposure. However, *ex vivo* microglial priming by prior stress, which had been extensively demonstrated in male rats previously, was not evident in microglia isolated from female rats. Nonetheless, microglia from stressed female rats displayed pro-inflammatory qualities such as reduced phagocytic activity similar to microglia of stressed male rats. Furthermore, the authors demonstrate female-specific peripheral cytokine priming. Taken together, these results raise the intriguing possibility that acute stress sensitizes neuroimmune processes via distinct mechanisms in males and females.

*Corresponding Author: Gretchen N. Neigh, PhD, Virginia Commonwealth University, 1101 East Marshall Street, PO Box 980709, Richmond, VA 23298, Voice: 804-628-5152, gretchen.mccandless@vcuhealth.org.

Results reported by Fonken et al. (2018) lead to several important questions. First, whether an identical cytokine environment in the brain can lead to divergent functional consequences for males and females needs to be answered in order for us to better understand the role of immune sensitization in the female bias in psychiatric illnesses. In addition, whether microglia are the primary driving force behind stress-induced cytokine priming in females needs to be assessed in future work. For example, the critical role of microglia in stress-induced immune-to-brain traffic in male mice is beginning to be elucidated using microglia depletion prior to stress exposure (McKim et al., 2017). Furthermore, in the study by Fonken et al. (2018), sex differences in stress-primed production of cytokines are present only in *ex vivo* experiments, but absent when outcomes are assessed in whole hippocampal tissue. This underlines the need to critically evaluate the tools via which potential sex differences are assessed in future studies. Some considerations are culturing conditions such as presence or absence of gonadal hormones in culture media, lack of cellular and cytokine milieu that would be present in *in vivo* experiments, and microglial isolation techniques, including anesthesia which can differentially impact males and females (Bekhbat et al., 2016), that may be impacting female microglia differently.

Previous literature on stress-induced priming in females is limited to two studies that examined the impact of stress on hippocampal expression of cytokines following either re-exposure stress (Hudson et al., 2014) or LPS (Pyter et al., 2013) as a secondary challenge. Notably, the nature of the secondary challenge has been reported to impact priming in some instances. Rats with a history of social defeat stress exposure show exaggerated cytokine mRNA expression upon a repeat exposure to social defeat; however, this potentiation does not take place if the secondary stimulus is LPS (Audet et al., 2011). Both Hudson et al. (2014) and Pyter et al. (2013) demonstrated hippocampal cytokine priming in adult male, but not female, rodents with a history of stress. Fonken et al. (2018) extend these findings and documents the occurrence of stress-induced *in vivo* priming of cytokine expression and sickness behavior in both male and female rats. The clinical implications of this work include the hypothesis that both men and women with depression will equally respond to anti-inflammatory treatments. To date, several studies have demonstrated increased microglial activation in depressed human subjects by imaging translocator protein (TSPO). While some of these studies have enrolled both male and female participants (Setiawan et al., 2015), it is not clear whether the extent to which microglia are activated in depressed individuals differs by sex. The Fonken et al. (2018) manuscript establishes that consideration of neuroimmune outcomes in males and females is essential and cannot be generalized between the sexes. Rigorous consideration of neuroimmune contributions to psychiatric and neurological disorders must include adequate representation of both sexes and/or appropriately tempered conclusions.

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