Biological Psychiatry: CNNI

# Commentary

# Can Immunopsychiatry Help in Understanding the Basis of Sex Differences in Major Depressive Disorder?

Robert Dantzer

While it is commonly recognized that the prevalence of major depressive disorder (MDD) is about twice as high in women than in men, the reasons underlying this difference are the subject of many of the controversies that surround the issue of sex and gender. At the sociocultural and economic level, it is important to remember that gender inequality significantly contributes to depressive symptoms in women. MDD affects mainly women who are younger, are nonwhite, are not currently married, are less educated, and have lower household incomes (1). Gender differences in resources and opportunities are amplified by the structural gender discrimination that exists in the adult work force and is associated with the gender wage gap. This structural gender discrimination has been found to contribute to mental health disparities at the population level in the United States. For example, the odds ratio for MDD, which is 2.43 in women whose income is less than their matched male counterparts, decreases to 1.20 when female income is greater than the matched male income (2). These macro factors should not minimize the importance of other micro factors, such as interpersonal violence, that are well known to play a role in the gender gap in depression. At the psychological level, it could be somewhat surprising to see that women who have larger and more intimate social networks than men still have higher rates of MDD, even though social support is generally considered as protective. A longitudinal study in opposite-sex twin pairs reveals that levels of social support by themselves do not explain the sex differences for MDD. This study indicates that women are more sensitive than men to the depressogenic effects of low levels of social support, particularly when they emanate from the co-twin, other relatives, parents, and spouses (3).

At the psychopathological level, efforts have been made to relate gender differences in mental disorders to differences in the latent internalizing and externalizing liability dimensions that frame key parts of the overall organization of DSM-5. Women would be more prone to internalizing disorders that characterize mood and anxiety disorders and men more prone to externalizing disorders that express themselves as antisocial and substance abuse disorders. Whatever the reality of this notion, we must not overlook its analogy with the folk view that depression is a disease of a weakened spirit that is more likely to afflict the weaker female sex than the stronger male sex.

The main limitation of most studies on the role of sex differences in MDD is that they consider depression as a diagnostic category, with the implicit assumption that the disorder is the same in women and men. This is not the case; there are important sex differences in both symptom profiles and comorbidities. Compared with men, women have a greater overall severity of depression, earlier age of onset, more somatic symptoms, and lower energy levels. In addition, women report comorbid symptoms of anxiety and eating disorders; men primarily report alcohol and substance abuse (4). In other words, women have higher rates of atypical and anxious depression than men.

Despite all the difficulties associated with the consideration of sex differences in mental disorders, biological psychiatrists are still tempted to relate sex differences in MDD to biological factors, such as the brain effects of sex hormones. This type of causal attribution is fueled, at least in part, by the well-known reproductive subtypes of depression that refer to episodes of depression occurring specifically during the premenstrual, postpartum, and perimenopausal phases in women (5). Sex hormones and neurosteroids have well-described effects on neurotransmission that can easily be accommodated to account for the mood fluctuations experienced by women at different stages of their reproductive lives. However, recent advances in biological psychiatry point to another set of potentially important players represented by immune factors. Depressed individuals show elevated levels of biomarkers of inflammation. Furthermore, the administration of inflammatory cytokines to naïve individuals induces symptoms of depression, while treatment with anti-inflammatory biologicals in inflamed individuals decreases symptoms of depression. The gradual invasion of the field of psychiatry by immunology, often referred to as immunopsychiatry, is not without importance for our understanding of the potential role of sex differences in depression (6). Women experience higher levels of inflammation and much greater autoimmune disease risk compared with men—up to eight times for lupus erythematosus, for instance. Acute inflammation induces symptoms of depressed mood and social disconnection that are more pronounced in women than in men and that are positively correlated to the increase in circulating inflammatory cytokines (7). In addition, factors associated with MDD, such as interpersonal violence, low socioeconomic status, and obesity, all elevate inflammation. In this context, the simplest explanation for sex differences in depression would be that women are more likely to become depressed because they experience more severe inflammation than men in response to psychosocial stressors, and even if this is not the case, their brains are

SEE CORRESPONDING ARTICLE ON PAGE 619

  https://doi.org/10.1016/j.bpsc.2019.04.011
 ISSN: 2451-9022

more sensitive to the detrimental effects of immune mediators. Neuroimaging studies offer a way to test this hypothesis because they provide a real-time measurement of brain regional activation in response to well-controlled stimuli. The study by Moieni *et al.* (8) in this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* makes use of this approach. Knowing that an intravenous injection of a low dose of endotoxin to volunteers induces anhedonia, one of the cardinal symptoms of depression, the research was designed to assess the impact of endotoxin-induced systemic inflammation on neural activation of the ventral striatum, an important structure in the processing of positively motivated behavior. Volunteers of both sexes were instructed to carry out a monetary reward task while placed in a functional magnetic resonance imaging scanner, and they were administered either saline or endotoxin in a double-blind procedure. As expected, endotoxin induced the de novo production and release of inflammatory cytokines, such as interleukin-6 and tumor necrosis factor, but there was no sex difference in their circulating levels. Compared with control subjects, endotoxin-treated volunteers showed a less marked activation of their ventral striatum in response to the expected reward, and this effect was more marked in female subjects than in male subjects. Furthermore, the decrease in striatal activation was proportional to the levels of circulating interleukin-6 and tumor necrosis factor in female subjects but not in male subjects. These results, obtained in a carefully set up, randomized controlled clinical trial of endotoxin versus saline, are important because they demonstrate for the first time the existence of sex differences in neural sensitivity to reward that could at least partly explain why women are more biologically at risk to develop depression when experiencing inflammation. One could easily imagine that this phenomenon is even more marked in individuals who are already chronically inflamed and whose innate immune system is primed by adversity, including low socioeconomic status and interpersonal violence.

Can we respond affirmatively to the question asked in the title of this commentary? The answer is probably "Yes, but…". Despite their strong appeal, the present results still need to be interpreted with caution because they reflect the belief that sexes cluster distinctively and consistently at opposite ends of a single gender continuum contrasting masculinity and femininity, whereas in fact, men's and women's attributes are likely to differ in ways that are continuous rather than categorical. Another issue that is largely ignored in this type of study is the implicit assumption that the perception and representation of the task are the same for both men and women in the presence and the absence of inflammation. This is not necessarily the case, especially in the context of the increased interoceptive sensory feedback created by inflammation. Females could simply become less engaged in the task when inflamed than their male counterparts simply because they are more sensitive to their bodily feelings. Muscatell *et al.* (9) did not report any sex difference in the observation that endotoxin-treated individuals become more sensitive to negative, threatening social experiences and positive, socially rewarding experiences. Further, Harrison *et al.* (10) reported that inflamed individuals become more sensitive to losses but not to wins in a monetary reward task. However, the low number of subjects in this last study precluded the investigation of any sex difference. All of this emphasizes the necessity of taking into account the possible interference effect of gendered norms with respect to phenomena such as nurturance, social threat, and interest in computer games when assessing the influence of sex in well-controlled experimental situations.

## Acknowledgments and Disclosures

This work was supported by National Cancer Institute Grant No. R01 CA193522, National Institute of Neurological Disorders and Stroke Grant No. R01 NS073939 (principal investigator, Annemieke Kavelaars), and an MD Anderson Cancer Center Support Grant (P30 CA016672).

RD has received honoraria from Danone Nutricia Research and Pfizer that are unrelated to the present work.

## Article Information

From the Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, Texas.

Address correspondence to Robert Dantzer, D.V.M., Ph.D., Department of Symptom Research, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030; E-mail: rdantzer@mdanderson.org.

Received Apr 26, 2019; accepted Apr 26, 2019.

## References

1. Chen YY, Subramanian SV, Acevedo-Garcia D, Kawachi I (2005): Women's status and depressive symptoms: A multilevel analysis. Soc Sci Med 60:49–60.
2. Platt J, Prins S, Bates L, Keyes K (2016): Unequal depression for equal work? How the wage gap explains gendered disparities in mood disorders. Soc Sci Med 149:1–8.
3. Kendler KS, Myers J, Prescott CA (2005): Sex differences in the relationship between social support and risk for major depression: A longitudinal study of opposite-sex twin pairs. Am J Psychiatry 162:250–256.
4. Marcus SM, Kerber KB, Rush AJ, Wisniewski SR, Nierenberg A, Balasubramani GK, *et al.* (2008): Sex differences in depression symptoms in treatment-seeking adults: Confirmatory analyses from the Sequenced Treatment Alternatives to Relieve Depression study. Compr Psychiatry 49:238–246.
5. Payne JL, Palmer JT, Joffe H (2009): A reproductive subtype of depression: Conceptualizing models and moving toward etiology. Harv Rev Psychiatry 17:72–86.
6. Derry HM, Padin AC, Kuo JL, Hughes S, Kiecolt-Glaser JK (2015): Sex differences in depression: Does inflammation play a role? Curr Psychiatry Rep 17:78.
7. 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.
8. Moieni M, Tan KM, Inagaki TK, Muscatell KA, Dutcher JM, Jevtic I, *et al.* (2019): Sex differences in the relationship between inflammation and reward sensitivity: A randomized controlled trial of endotoxin. Biol Psychiatry Cogn Neurosci Neuroimaging 4:619–626.
9. Muscatell KA, Moieni M, Inagaki TK, Dutcher JM, Jevtic I, Breen EC, *et al.* (2016): Exposure to an inflammatory challenge enhances neural sensitivity to negative and positive social feedback. Brain Behav Immun 57:21–29.
10. Harrison NA, Voon V, Cercignani M, Cooper EA, Pessiglione M, Critchley HD (2016): A neurocomputational account of how inflammation enhances sensitivity to punishments versus rewards. Biol Psychiatry 80:73–81.