Inflammation and Depression

Why do women have a higher risk for depression than men?

BY MONA MOIENI

AROUND THE WORLD, more than 350 million people suffer from depression [1]. It is the leading cause of disability worldwide [1], and it has been estimated that the annual cost of depression in the United States is about $80 billion due to health care costs and lost productivity [2]. While both men and women can become depressed, women are twice as likely as men to experience depression [3-6], whether depression is defined as a diagnosed mental disorder or depressive symptoms [7]. This sex difference in rates of depression is well-documented and cross-cultural [6, 8]. It is also not explained by sex differences in reporting or recalling of symptoms or seeking help for symptoms [9]. In fact, this sex difference in depression has been described as one of the most robust findings in psychopathology research [10, 11].

Why are women so much more likely to get depressed than men? Researchers have proposed several theories to explain these sex differences in depression. One of the many factors thought to contribute to the sex difference in depression is women's greater dependence on social relationships. That is, women tend to prefer close emotional communication and social intimacy, and it has been suggested that this greater emphasis on close personal connections in women can interact with stressful negative life events (especially social ones) and other factors (e.g., anxiety, hormonal changes) to result in greater rates of depression in women [10].

What else may be causing this sex difference? Another place to look to understand this difference would be to understand the relationship between inflammation, which is our immune system's first line of defense against injury or infection, and depression. In response to injury or infection, the body releases proinflammatory cytokines, which help the body fight off the injury or infection. In addition to fighting off infection, proinflammatory cytokines also communicate with the brain [12, 13] to cause a set of symptoms called "sickness behavior," which includes symptoms such as fatigue, anhedonia (i.e., inability to experience pleasure), and increased sensitivity to pain [14-17]—symptoms that we typically associate with being sick. It is thought that this response is adaptive because it allows the body to focus its energy on recovering from the illness rather than spending its energy on other things, so that your body can recuperate.

Interestingly, these sickness behavior symptoms strongly resemble symptoms observed in depressed individuals. In fact, experimental work has also shown that when you give a healthy group of people a substance that causes inflammation,

they show increases in depressed mood [18] as part of the sickness behavior symptoms. Another consequence of inflammation that is particularly relevant to understanding sex differences in depression is that inflammation can also trigger social withdrawal [14, 17] and lead to feelings of social disconnection [19, 20]. Feelings of social disconnection or loneliness play a critical role in the onset and perpetuation of depression [21], and as mentioned earlier, social factors may be key in understanding the sex differences in depression. Thus, it may be important to understand social psychological changes due to inflammation in order to better understand the relationship between inflammation and depression, particularly to understand why women are so much more likely than men to develop depression.

Other work also supports the idea that inflammation may be contributing to depression [13, 22]. For example, individuals with inflammatory diseases are far more likely to experience depression [23-25], and patients with major depression who are otherwise healthy have been found to have increased inflammatory markers [26]. There are also sex differences in inflammatory processes, such that women show greater inflammatory reactivity [27], and women are also two to nine times more likely to develop autoimmune disorders, which are often associated with increased inflammation [28, 29]. Thus, there seems to be support from multiple lines of research for this idea that inflammation may be leading to the development of depression for some patients and that understanding this relationship may be helpful in understanding why women develop depression more than men.

While we know that inflammation can lead to depressed mood and feelings of social disconnection, and understanding the relationships between these things may help us better understand sex differences in rates of depression, the majority of the experimental work looking at the effects of inflammation on sickness behavior in humans has surprisingly focused on samples consisting of only men. By studying the differences between men and women in this kind of research, we may develop a better understanding of some reasons why women are more at risk for developing depression. Thus, our research group at UCLA conducted a study to help fill this gap in the scientific literature. We examined both men and women in order to determine whether there are sex differences in the effect of inflammation on depressed mood and social disconnection, which may ultimately have implications for understanding sex differences in depression.

In our study, we had a large sample (115 total subjects) made up of both men and women. All participants came to the UCLA Clinical and Translational Research Center (CTRC) in the morning, and about 90 minutes after they got to the CTRC, a nurse gave them either a placebo or a substance known to cause an inflammatory response in a safe, acute manner. This inflammatory-inducing substance is called endotoxin and it is derived from the cell wall of the *E. coli* bacteria. When given to human subjects in a controlled setting, it triggers a short-lived inflammatory response in a safe manner. By experimentally inducing inflammation using endotoxin, we could look at whether inflammation *causes* changes in depressed mood and social disconnection, and thus we could examine whether there are sex differences in biological indicators of inflammation and self-reports of depressed mood and feelings of social disconnection in response to inflammation. Because women are more likely to experience depression, are more sensitive to social cues, and are more likely to develop certain inflammatory disorders, we expected that women would show greater inflammatory responses, depressed mood, and feelings of social disconnection in response to the endotoxin compared to placebo.

The inflammatory effects of endotoxin are fairly acute; so, the study lasted only one day. Endotoxin reaches its inflammatory peak about 2 hours after injection, and participants were released from the study 6 hours after the injection, once their symptoms returned to normal. All participants left the study feeling as well as they did when they started. Throughout the study day, we also measured the things we were interested in examining in this study. Thus, participants had their blood drawn so that we could look at inflammatory measures (i.e., proinflammatory cytokines). We were also interested in how depressed participants were feeling, and so we asked them to rate, for example, how "sad"

and "blue" they felt. Because we were interested in feelings of social disconnection, we asked them how much they would agree with statements like "I feel lonely" or "I feel disconnected from others."

As expected, women, compared to men, reported greater depressed mood in response to the endotoxin. In addition, women also reported greater feelings of social disconnection in response to the endotoxin than men. Finally, although we expected that women would show greater inflammatory responses compared to men, we did not find that to be the case. We found no differences between men and women in the increase in inflammatory measures in response to endotoxin. However, we did find that for the women in our sample, those who showed greater increases in inflammation also reported feeling more socially disconnected. This relationship between the magnitude of the inflammatory response and feelings of social disconnection was not present for men.

What do these findings mean for understanding sex differences in depression? First, we found that women showed greater increases in depressed mood in response to an inflammatory challenge. This finding may mean that women are more sensitive to the mood changes that may accompany an increase in inflammation. Inflammation is thought to contribute to depression in at least some patients; thus, this could potentially mean that women are developing depression more often than men in part because they could be more sensitive to the emotional changes that can result from inflammation.

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We also found that women in our study reported greater feelings of social disconnection in response to an inflammatory challenge. Additionally, greater increases in inflammatory activity were directly associated with greater feelings of social disconnection in women, but not in men. This may also help us understand why women develop depressive disorders more often than men. As discussed earlier, feelings of social disconnection can contribute to depression, and it has been suggested that one reason that depression occurs more often in women than men is women's greater dependence on social relationships. Here, we found that women may be more sensitive to the social psychological changes that accompany inflammation, which may also be influencing women's vulnerability to developing depression.

In addition to providing insight into the sex difference in depression, this study may also have other impli-

cations for women's health. Because these findings suggest that women are more sensitive to the emotional and social changes that accompany increases in inflammation, this may indicate that women with chronic inflammatory disorders may be more susceptible to developing depression. Of course, further work would need to be done in order to make any clinical recommendations, but the current findings would support the idea that physicians may want to especially monitor women with chronic inflammatory disorders (e.g., rheumatoid arthritis), as they may have a heightened risk for developing depressive disorders.

These findings are particularly important because the vast majority of studies looking at the effect of inflammation experimentally in humans have been done in samples exclusively made up of men. Given that we found sex differences in our study, it would be important for future studies looking at the emotional and social consequences of inflammation to include women in their samples. Because the participants in our study were young (mean age = 24) and healthy, future studies should be done in older and clinically depressed samples in order to better understand the findings from this study.

Indeed, it would be important to replicate and extend these findings before making any firm conclusions about the implications for depression. However, when combined with future studies, these findings may help us understand the relationships between inflammation and depression, as well as why women are so much more likely than men to develop depression. Ideally, our findings will be built upon by other researchers, and together, we can build a rich, nuanced understanding of the complex relationships between sex, inflammation, social factors, and depression. Ultimately, a better understanding of these relationships may hopefully allow us to help those at-risk for and living with depression.

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