Why is anxiety more common in women? Investigating sex differences in threat and safety learning

Anxiety-related disorders like post-traumatic stress disorder (PTSD) are up to twice as common in women as in men but the reasons behind this remain unclear. People with PTSD often experience negative emotions like fear when reminded of a prior trauma by cues in their environment. This can happen even if the environment that they are in is safe (e.g. a war veteran back at home watching television) and the cues are harmless (e.g. the war veteran hearing gunshots on the television).

Psychological therapies can help people with PTSD to inhibit their fear by repeatedly exposing them to cues that were associated with prior trauma but now no longer pose a threat (e.g. replaying the sound of gunshots to the war veteran). This process is known as extinction and, interestingly, fear regulation through extinction is impaired in females compared to males. People with PTSD also show deficits in their ability to distinguish between trauma-related cues (e.g. the sound of gunshots) and similar cues not associated with the traumatic experience (e.g. other loud noises). This impaired fear discrimination, or fear generalization, has been proposed as a biomarker of PTSD. So, if females show impaired extinction, do they also show more fear generalization?

We investigated this issue using a rodent model by examining differences between male and female rats in an auditory fear discrimination task. Rats were exposed to two sounds: the ‘conditioned stimulus’ (CS+) that was always paired with a mild electric shock, and a different sound that was never paired with shock (CS-). Over the course of training the CS+ should predict the shock and become a ‘threat’ cue, while the CS- should predict that the shock won’t occur and become a ‘safety’ cue. If the rats successfully discriminate between the CS+ and CS- by the end of training then they should show more fear behaviour in response to the CS+ compared to the CS-.

This is what we found in males: after one day of training males didn’t show discrimination but after 2-3 days of training they did discriminate between the CS+ and CS-. In females, however, we saw the opposite pattern of results: after one day of training they showed discrimination but after 2-3 days of training they didn’t discriminate (i.e. they generalized) between the CS+ and CS-. We also conducted other experiments that ruled out sex differences in pain sensitivity and unlearned fear behaviour as alternative explanations for our results. Instead, they are more likely due to differences in how males and females process cues predicting threat or safety.

These sex differences in fear discrimination and generalization warrant further studies on the underlying biological mechanisms involved, which, in turn, will lead to a better understanding of why anxiety disorders are more common in women than in men.

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