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Commentary

Complex associations among sex, anxiety and pain

Sex differences in pain have been well-documented. Women are at greater risk for many clinical pain conditions, which has led researchers to investigate responses to controlled experimental stimuli in an effort to identify potential sex differences in pain processing. Sex differences in pain sensitivity have been widely investigated, with findings consistently demonstrating that women report increased pain in response to noxious stimuli [4]. Although the magnitude of the differences varies across studies and across pain measures [7], the direction of sex differences in pain sensitivity is remarkably consistent [4,6].

Multiple biopsychosocial mechanisms contribute to sex differences in pain sensitivity, including gonadal hormones, genetic factors, and multiple psychological variables. Given their association with pain and their greater prevalence among women, negative mood states, such as anxiety and depression, represent plausible contributors to sex differences in pain. Several studies have, in fact, reported that anxiety is associated with pain in a sex-dependent manner and somewhat surprisingly anxiety is more strongly associated with both clinical pain and experimental pain sensitivity among men than women [3,4]. However, anxiety includes multiple constructs (e.g. general anxiety, pain-related anxiety, anxiety sensitivity). Whether different anxiety-related constructs show varying sex-dependent associations with pain responses has not been systematically explored. In the current issue of *PAIN*, Thibodeau et al. [9] address this question in an investigation of the association of multiple anxiety-related variables with heat and cold pain responses in healthy adults. As in prior research, anxiety was associated with experimental pain responses in a sex-dependent manner; however, the pattern of associations varied across different pain and anxiety measures.

Consistent with the existing literature, women showed lower pain thresholds and tolerance than men, with moderate to large effect sizes; however, ratings of suprathreshold heat and cold pain stimuli did not consistently differ across sex (generally small effect sizes). Sex differences in anxiety levels did not emerge for measures of general anxiety, fear of pain or pain-related anxiety; however, women reported greater anxiety sensitivity. To probe for sex-specific associations between anxiety and pain responses the authors conducted separate regression analyses for women and men. To identify which constructs explained unique variance in pain responses, they entered all four anxiety constructs (trait anxiety, fear of pain, pain-related anxiety, and anxiety sensitivity) into the regression models. In contrast to previous findings, anxiety measures were more strongly related to heat and cold pain tolerance among women than men. Specifically, higher fear of pain predicted lower heat and cold pain tolerance in women but not men, while higher anxiety sensitivity unexpectedly predicted greater heat and cold pain tolerances in women. However, consistent with prior research, anxiety measures predicted heat and cold pain ratings more strongly in men than in women. In particular, anxiety sensitivity was positively associated with heat pain ratings in men, while fear of pain and pain-related anxiety predicted ratings of less intense and more intense cold pain stimuli, respectively, in men. These findings show that the pattern of sex-dependent associations between anxiety and pain sensitivity is influenced not only by the anxiety construct measured, but also by the specific pain endpoint (i.e. tolerance vs. pain ratings).

The neurobiological mechanisms underlying sex-specific associations between anxiety and pain remain poorly understood; however, several possibilities are worth considering. For example, analysis of sex differences in brain activation in response to emotional stimuli found that women generally showing greater activation in several brain regions in response to negative emotions, including the amygdala, left thalamus, left caudate, and medial prefrontal cortex [8]. Such differences in cerebral responses could sex-specifically modulate pain-related brain activation, thereby altering pain experiences differentially for women and men. Moreover, catechol-O-methyltransferase (*COMT*) genotype was associated with neural responses to fear-related stimuli in women but not men [2]. Because *COMT* has also been associated with pain sensitivity and risk for development of chronic pain [1], such sex-specific associations between *COMT* and anxiety-related responses could contribute to sex differences in pain-anxiety associations. In addition, estrogens influence both stress responses and pain and represent another mechanism that could explain sex-dependent associations between anxiety and pain [5].

Although the findings of Thibodeau et al. [9] derive from a study of experimentally-induced pain in healthy adults, the potential clinical implications of sex differences in pain-anxiety associations merit consideration. As noted above, anxiety has been associated sex-specifically with clinical pain in chronic pain populations, such that men with greater pain-related anxiety also reported greater clinical pain severity, but no such association emerged for women [3]. Interestingly, Edwards et al. [3] also found sex-dependent associations between pretreatment anxiety and pain reductions in response to various medical, interventional and psychological treatments. For women, lower pre-treatment anxiety predicted greater pain reductions in response to treatment, but the reverse direction of association emerged for men. These findings suggest that pain-related anxiety differentially influences treatment responses among women and men. Whether treatment aimed at reducing anxiety would impact pain differently across sex has not been determined. Based on the findings reported by Thibodeau et al. [9], the answer to this question may depend on the type of anxiety being targeted as well as the aspects of pain being measured (e.g. pain ratings vs tolerance).

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Despite the relatively complex pattern of results reported, the findings of this study generate several actionable conclusions. First, when exploring associations between anxiety (and potentially other psychosocial factors) and pain, investigators should consider the sex of the individual as a potentially important moderator variable. Second, there are multiple anxiety-related constructs. As their associations with pain appear to vary, a broad-based assessment of anxiety is recommended. In particular, pain-related anxiety constructs are more strongly associated with pain responses; thus pain-related anxiety should be assessed. Third, sex-differences in the association between anxiety and pain depended on the pain measure, with one pattern emerging for pain tolerance and a completely different pattern observed for pain ratings. Although the reasons for these patterns remain unclear, the findings highlight the importance of obtaining multiple pain measures across multiple stimulus intensities. Despite its limitations (e.g. inclusion of only healthy young adults, use of only cutaneous thermal stimuli, a male experimenter conducted all sessions) which are acknowledged by the authors, the study by Thibodeau et al. [9] provides a model for research investigating the association between anxiety and pain. By adopting these approaches, future investigations will be able to elucidate both the mechanisms and clinical implications of sex-specific associations between anxiety and pain.

Conflict of interest statement

Roger Fillingim is a consultant and equity stock holder in Algynomics, Inc., a company providing research services in personalized pain medication and diagnostics.

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Roger B. Fillingim
University of Florida, USA
E-mail address: RFillingim@dental.ufl.edu