Gender Differences in Pain

Role of Anxiety

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Gender differences in pain responsiveness, like gender differences in other aspects of behavior, remain fascinating, enigmatic, and, sometimes, vexing. Fillingim and Maixner have tackled this issue in heroic fashion and laid before us both a comprehensive review of the literature and a framework for thinking about some of the relevant concerns.

It would be easy to say that pain behavior is determined by various components and leave it at that. To do so, however, would stifle the sort of careful thought and meticulous research that the subject deserves. Moreover, it would lead to an injustice against individuals suffering from pain disorders that are disproportionately linked to gender, since increased understanding of the neural and behavioral factors that underlie gender differences in pain responses may also shed light on the factors that establish and maintain their pain disorders.

This commentary will deal with selected aspects of two issues inspired by the Focus article: first, gender differences in nonsensory factors affecting behavior in the pain laboratory and, second, the critical role of gender differences in anxiety.

LABORATORY-INDUCED PAIN

Fillingim and Maixner properly point out the large degree of interobserver variability associated with perceptual measures such as pain threshold, pain tolerance, or the slope of psychophysical power functions and they note the potential role of such variability in contributing to the discrepancies across studies. It may be tempting to see such variability as a condemnation of the use of traditional psychophysics in the assessment of pain. Wall,[37] for example, wrote:

> The delight of psychophysicists is their ability to establish thresholds and to measure lawful relations between stimulus intensity and the strength of sensation. They have obviously been very successful in vision and hearing. There have been persistent attempts to establish thresholds and scales relating experimental stimuli to evoked pain. The results are farcical in their wild variability when compared to vision, hearing, smell, taste, and touch. The persistent failure of subjects to relate stimulus intensity to pain intensity is one of the strongest reasons to question the classical attempt to group pain with the familiar sensations evoked by external sources.

As noted elsewhere,[27] "wild" variability across subjects is not specific to pain. Vibration sensitivity on the finger had a standard deviation of about 3.2-fold in terms of amplitude. Visual thresholds for a group of subjects in a dark-adaptation study varied more than four-fold. Olfactory sensitivity spanned a twenty-fold range. Even among a large, common group of subjects in which those with inconsistent performance were eliminated from consideration,[16] visual thresholds spanned a twenty-eight-fold range, pure-tone thresholds a six-fold range, and electrocutaneous thresholds also varied six-fold.

Within-subject variability tends to be much smaller and, consequently, indicates that measures such as pain threshold and tolerance are reliable. Moreover, those whose threshold or tolerance are high for one stressor, such as trains of electrical shock, tend to have high thresholds, as well, for other stressors such as cold and pressure, providing evidence for discriminant validity.[14]

It is unlikely, however, that all subjects interpret the concept of threshold or tolerance in the same way, even when presented with standardized instructions in a lab-

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oratory task. Threshold, while subject to both sensory and motivational influences, emphasizes a decision regarding a shift from innocuous to noxious sensation. Tolerance, although ostensibly also a sensory decision, is more evidently open to affective and cognitive contributions.[33] These measures may interact with the type of pain stimulus and, particularly important for our present considerations, with gender.

Several years ago,[28] I described an experiment in which 20 male and 20 female subjects were presented with three different forms of experimental pain: electrical shock, the cold pressor task, and the constant pressure algometer. Measurements were obtained for pain threshold and tolerance. For each of these points, subjects were presented with an additional task: to use a numerical scale, extending from 1 (slight pain) to 10 (very severe pain), to indicate how painful the stimulus was when they indicated it had become painful and when they requested that the stimulus be halted.

Although this seemed to be an almost irrational exercise, the results were extraordinarily revealing. First, the ratings varied with the nature of the noxious stimulus. For shock, subjects reported that their pain threshold corresponded to a rating of 1.8, whereas for cold and pressure they waited until they were more certain of the shift from neutral or nonpainful and gave mean ratings of 3.8 and 3.7, respectively. For tolerance, the differences were even more marked; the mean rating when subjects felt they had experienced as much pain as they were willing to endure was only 5.9, whereas the corresponding values for cold and pressure were 7.9 and 7.1.

More revealing, yet, were the gender differences in this behavior. The women subjects called a halt to the presentation of electrical shock when the self-described pain was at a level of about 5 on the 10-point scale (moderate), compared to nearly 7 for the men. That is, the women knew, quite well, that what they called "tolerance" was not at all the maximum level they could tolerate. Rather, it appeared that they were signaling that this was the upper limit that they wished to receive and, indirectly, saying something to the effect of, "I don't really want to play your game."

As noted above, for cold and pressure, the self-reported pain at tolerance was higher for both men and women than it was for shock. Although there was a tendency for women to still stop sooner than men, the differences were much smaller. What is special about shock? Clearly, there are a number of qualitative differences between the subjective sensations produced by electrical stimuli compared to thermal and mechanical stressors, but there are likely to be pivotal affective and cognitive differences as well. In particular, there may be differences in anxiety associated with exposure to such a relatively strange and potentially perilous stimulus.

In a subsequent experiment, we found that state anxiety prior to participating in an experiment involving electrical shock was 39.7 for women, compared to 33.3 for men ($P < .05$). Moreover, in a study in which electrical pain thresholds were determined on three separate days, the level remained relatively stable for men, while that for the women increased more than 50%. These findings reinforce the notion that males and females may bring different levels of anxiety to the pain laboratory, particularly in studies involving just a single testing session and unfamiliar stimulus conditions. Put another way, some, or even most, of the studies reviewed by Fillingim and Maixner that evidenced gender differences in pain responsiveness (including some of my own) may have confounded anxiety with pain.

A number of other results from my laboratory provide further evidence that setting, cognition, and affect may bias the determination of gender differences in pain reactivity. For one, men and women come into the laboratory with different expectations of their pain tolerance. When asked to indicate where, on a hypothetical scale going from 0 to 100, their pain tolerance would be located, a large group of men gave a mean response of 74. The mean for a corresponding group of female subjects was 65 ($P < .001$).

In a recent paper, Lautenbacher and Rollman[20] reported that women had significantly lower pain and tolerance thresholds for electrocutaneous stimulation than did men. Women had a state anxiety measure of 36.4 on the State-Trait Anxiety Inventory, compared to 33.2 for men (the variability was substantial and the difference was not statistically significant). The same subjects showed no significant difference in their pain thresholds at the hand or foot for heat produced by a Peltier thermode—a less threatening stimulus.

GENDER, PAIN, AND ANXIETY

Is there other evidence for the effects of anxiety on pain threshold and tolerance? Is there evidence for significant gender differences in anxiety? The answer to both queries is in the affirmative.

Consider a few of many examples relevant to the first question. Anxiety enhanced pain responsivity in the laboratory and certain instructions increased pain tolerance for men but decreased pain threshold and pain tolerance for women.[10] Anxiety disrupted the use of self-control strategies in dealing with cold pressor pain.[5] Patients who scored high on pain-related anxiety tended to overpredict new pain events during physical examination.[21] Anxiety-evoking instructions increased laboratory pain ratings, electromyographic activity, and facial grimaces.[9] High scores on anxiety, depression, and fear were associated with low pain tolerance.[31] Patients suf-

fering from major depression showed a negative correlation between pain threshold for electrical pulses and levels of anxiety.[1] Pain threshold correlated negatively with scores on the Taylor Manifest Anxiety Scale.[35]

To be sure, the relationship between anxiety and pain is not a simple one, nor has it always been found. Arntz and DeJong[4] suggested that attentional focus, rather than anxiety per se, affected the reaction to electrical stimulation. Al Absi and Rokke[3] hypothesized that anxiety that is relevant to the source of pain exacerbates perceived discomfort, whereas anxiety that is irrelevant to the source of pain reduces the pain experience. The first part of the hypothesis was confirmed; subjects who were highly anxious about cold pressor pain reported the most pain when exposed to that stressor.

Gender differences in anxiety have also been frequently reported. Teenage girls had a significantly higher level of trait anxiety than boys and showed less evidence of behavioral control in situations involving physical injury.[26] Young adult, middle adult, and elderly women had higher trait anxiety than men.[34] Women were more likely than men to report anxiety in a variety of medical situations.[29] Female chronic pain patients were more likely to manifest anxiety disorders.[11] Women patients preparing for coronary arteriography scored significantly higher than men in both state and trait anxiety.[30] Women had significantly higher preoperative anxiety prior to coronary bypass surgery.[32] Other studies[15] report gender-related differences in cognitive coping patterns and psychoendocrine responses to pain.

These gender differences may be influenced by psychosocial factors, such as expected sex roles, and there is evidence, from longitudinal studies, that men and women are now more equal in the incidence of anxiety and depression than they were in studies conducted some decades ago.[24] The gender differences in anxiety are almost certainly also affected by biological factors, since the animal literature is replete with studies showing an effect of sex on anxiety. Female rats showed more defensive behaviors to potential threat than did males.[8] The serotonin agonist 8-OH-DPAT was more potent in female rats than in male ones in reducing a number of anxiety-related behaviors caused by placing the animal near a compartment containing a natural predator (cat).[7] Blanchard et al.[6] concluded that "sex effects must be considered in studies of the pharmacological control of defensive behaviors."

Recent studies have shown the gender-selective effects of anxiety-related stress-induced analgesia in animals. Female rats showed lower levels of analgesia mediated by endogenous opioids after exposure to a predator and significantly greater anxiogenic responses.[17] Female mice exhibited less opioid-mediated analgesia following physical restraint.[19] Male laboratory mice displayed significantly greater levels of both opioid and nonopioid stress-induced analgesia than females.[18] Mendez et al.[23] demonstrated that male mice exhibited markedly greater levels of kappa opioid-mediated analgesia following stress, and Akinci and Johnston[2] reported much lower binding of MK-801 on the NMDA subclass of glutamate receptors located in the forebrain of adult females, when mice of both sexes underwent equivalent cold-water swims. As in the psychophysical data, the variables of pain, analgesia, anxiety, and gender are intertwined, perhaps inextricably.

IMPLICATIONS OF THE PAIN-ANXIETY RELATIONSHIP

The role of affective and cognitive factors in pain is well-established.[22] Still, despite the emphasis on the assessment of multiple components of the pain experience, whether by questionnaire or multiple visual analog scales,[25] we are still uncertain to what extent differences in the way male and female subjects react to experimentally induced pain is due to differences in sensory factors or differences in distress. Likely, it is both and considerably more. Clarification of this distinction is essential, not only to understand performance differences in the laboratory but to identify etiological factors in the establishment of such gender-associated maladies as temporomandibular disorders, fibromyalgia,[13] or headache and to select appropriate pharmacological and psychological strategies in their management.

Pain, chronic ill-health, and life changes are interwoven in an intricate pattern, with anxiety as the "silent partner."[36] In 1981, Gross and Collins[12] observed that, for both anxiety and pain, "self-report data share common descriptors, physiological data reflect a general activation of sympathetic arousal, and overt-motor behaviors share common response characteristics. Likewise, the treatments for anxiety and pain are related for both medical and psychological interventions. (There is) a need for direct comparisons of anxiety and pain symptoms." That need is all the more compelling if we hope to elucidate how gender interweaves in this motif.

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