Topical review

Deconstructing sex differences in pain sensitivity

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1. Introduction

Aristotle erroneously believed that women had fewer teeth than men, even though this preconceived notion could easily be tested with a simple measurement [2]. Today, women are proclaimed “pain sensitive”. But despite several investigations and best intentions, this view is too simplistic given the myriad metrics that comprise “sensitivity”. Although there may be a relationship between lower pain thresholds and a greater incidence and prevalence of many debilitating chronic pain conditions in women, the data are not definitive and there certainly are several chronic pain conditions more prevalent in men\textsuperscript{[5,15,19,42]}. From a socio-cultural perspective, ascribing higher pain sensitivity to any group can lead to incorrect assumptions such as disposition to “heightened somatic tendencies” [6,10]. This disparity has important sociological consequences with a strong link to occupational sex inequities [3,31]. Moreover, women are often undertreated for their pain [30,41].

In this review, we explore the fundamental questions as to whether men and women (1) experience pain similarly, and (2) are similarly sensitive to noxious stimuli. The answers to these questions are essential to our understanding of mechanisms that underlie sex differences in acute and chronic pain, and effective treatment for both sexes. Yet, studies of these fundamental issues have been riddled with variability owing, in part, to the lack of standardized measures, poor control of context, and other experimental variables. Therefore, to understand sex differences in acute and chronic pains, we revisit the factors that should be used to designate “sensitivity” and suggest a paradigm shift towards a mechanistic understanding of sex differences in pain.

2. The evolution of the “pain sensitivity” concept

Historically, assumptions about pain-sensitive individuals have been grounded in ideas about physical or moral strength. High pain sensitivity has been traditionally viewed as a weakness, and people who were stoic or less pain sensitive were thought to be strong. Many cultural beliefs hold that men are less sensitive to pain than women [9,10]. These impressions have lingered, despite evidence of great intersubject variability, cultural differences, and complexity in assessing pain sensitivity. In a 1940 psychophysical study of sex differences in metabolic responses to temperature, Hardy and Du Bois [21] noted the dearth of psychophysical studies that took into account sex differences, with most measuring pain responses only in men, assuming that findings could be generalized to both sexes. In 1997, a thought-provoking review by Berkley [5] underscored the importance of sex differences in pain research. She reported the major discrepancies in the literature where sex was construed as a covariant of no interest or “irrelevant variable”. She also highlighted that most studies either did not report the sex of their subjects or studied men exclusively. This landmark review by Berkley [5] and a 2007 consensus report on studying sex and gender differences in pain clearly stated that “we recommend that all pain researchers consider testing their hypotheses in both sexes”, and provided a variety of measures to be used for such testing [19]. However, these recommendations have not been implemented widely (partly owing to practical issues) and thus most studies of sex differences of pain simply rely on threshold testing to capture pain “sensitivity”.

3. Are women truly “pain sensitive”?

There is now growing interest and research activity on sex differences in pain [35,39,40]. In general, many studies have reported lower pain thresholds, less pain tolerance, and greater evoked pain in women compared with men [15,42]. However, there is significant variability between studies, results are riddled with small effect sizes [5,50], and despite much effort, pain sensitivity measures...
and chronic pain conditions among women have not been clearly and consistently linked [5,27]. Despite heterogeneous findings in these studies, the predominant view that still persists is that women are the pain-sensitive sex. A recent systematic review of 172 pain and sex studies bring more clarity to this issue by demonstrating that sex differences are highly variable and only exist for some types of pain measures. Whereas lower pressure pain thresholds and thermal/pressure pain tolerance in women is variable between studies, only a small percentage of studies showed sex differences for cold/muscle/ischemic pain thresholds, or for chemical or ischemic pain tolerance [39,40]. Furthermore, some studies have shown that women exhibit greater temporal summation and experimentally-induced secondary hyperalgesia and less pronounced diffuse noxious inhibitory controls (DNIC analgesia) than men, although other studies have not concurred with this sex difference [40]. The take-home message from these meta-analyses is that sex differences in pain do represent trends, but, in most cases, the findings are more nuanced than the conclusions. When significant, women do show greater sensitivity, but these effects are prominent only in specific experimental modalities.

4. Women are more perceptive than men across multiple sensory domains

As with pain, sex differences in other sensory modalities are mixed across studies [44], but when significant, very often women show greater sensory detection acuity than men [1,4,32]. It has been shown that women detect small changes in temperature with better acuity than men, with steeper within-session stimulus–response functions [14]. This effect was linked to a high responsiveness to pain, implicating a better sensory discrimination of pain in women, rather than a difference in attitude or emotional response to pain. Sex differences in pain seem to parallel findings of sensory perception in other sensory domains, including thermal, olfactory, gustatory, and visual. For example, some studies have shown that more women than men are “super tasters”[4]. Women also have greater olfactory acuity [12,32,47] and better tactile discrimination than men [8,18,45]. Furthermore, it has been shown that women have better visual color discrimination [1,37] and are better at distinguishing shades in the center of the color spectrum (ie yellows, greens, and blues) [38]. Furthermore, molecular genetics suggests that a large proportion of women have more classes of retinal photopigments than men, in general, which allows them to perceive more colors [28,43].

5. Sex differences in response to suprathreshold and dynamic pain stimuli

A phenomenon that often distinguishes chronic pain patients and shows sex differences is the temporal summation phenomenon where repetitive brief suprathreshold stimuli evoke greater pain over time and after-sensations in women [40,46] and chronic pain patients [16,20]. This effect has been attributed to central excitability or wind-up of nociceptive inputs [33]. Another explanation based on our studies is that women are more responsive to dynamic or rapidly changing noxious stimuli. We found that women report more pain than men during the dynamic phase of stimulation, such as at stimulus onset and when stimulus temperatures are increasing [23,25] (Fig. 1).

Suprathreshold stimuli that evoke temporal summation have a dynamic component, as do stimuli used to determine pain tolerance and thresholds with the “method of limits”. Thus, sex differences in response to changing noxious stimuli may contribute to the overall perceptual differences in pain perception between men and women. Conversely (in contrast to longer after-sensations in women reported by others [20,46]), we found that compared with men, women showed greater adaptation to sustained suprathreshold noxious stimuli and greater habituation to repeated long duration stimuli (Fig. 1) [13,23,24]. This suggests that even though women may have lower thresholds for pain, they appear to have mechanisms to modulate and cope with pain more effectively than men over time. The mechanisms underlying this sex difference may involve different engagements of top-down controls or pain modulatory systems [49]. Interestingly, we found that the temporal dynamics of pain in women were more similar to the temporal pattern of sharp pain that is associated with fast detection systems attributed to A-β fibers. These sensations were robustly evoked at stimulus onset, but dissipated during the latter half of the stimulus [23]. When tested with a stimulus profile where the temperature dynamically increased throughout the stimulus, women reported more sharp pain sensations than men, and this effect was seen in hairy, but not glabrous, skin [25]. In contrast, the temporal pattern pain responses in men were similar to the pattern of burning sensations attributed to C-fibers, which are evoked throughout the stimulus duration [22,23,25]. These findings implicate a divergence in pain subsystems in mediating temporal aspects of sex differences that may be associated with two distinct types of afferent inputs. We propose that such mechanistic models based on pain pathways and mechanisms combined with genetic and neurobiological factors will direct us to the causes of sex differences in pain and their variability across findings.

6. Genetic and psychosocial factors underlying sex differences in pain perception

Two prominent factors contribute to the occurrence and the variability in sex differences in pain perception: psychosocial factors and genetic sexual variance. Stereotypes ingrained by archea sociological and cultural constructs can influence pain perception [48], but the effect is variable across studies [40]. Other psychological and social factors, such as emotional states and catastrophizing, may also contribute to sex differences in pain responses, but, again, findings are inconsistent across studies [40]. Thus, whether greater sensory acuity results in, or is affected by, psychosocial factors, and whether this link causes maladaptive psychological and neurobiological response to pain, such as greater hypervigilance [11] and chronic pain, is not clear. However, greater sensory acuity for pain may allow a better instantiation of noxious stimuli [14] and thus could be advantageous for survival in situations requiring rapid response to physical harm.

Genetics has an important role in determining pain responsiveness, such as exemplified by the greater pain sensitivity and higher expression of the MC1R gene in women with red hair [28,34]. It is possible that genetic factors that contribute to pain sensitivity may vary in women more than men resulting in marked inter-individual variability in pain detection [36]. Another hypothesis is that a genetic factor underlying sex differences contributes to heightened sensory detection of all sense perception. A recent systematic study of more than 500 healthy volunteers [17] showed that acuity across multiple sensory functions is linked to heritable genes that underlie sensory traits. For instance, women had better detection of cold, warm, tactile stimulus onset [17]. Thus, women may have a genetically determined sensory perceptiveness of all sensory domains, perhaps including pain. This type of genetic variability can be studied explicitly using genomic tools and in the future may provide insight into the contribution of such factors. Taken together, genetic and psychosocial factors likely do not independently mediate sex differences in pain perception, but may influence perception in combination with neurological factors such as brain organization.
The term “sensitivity” is often used interchangeably to mean “threshold”, thereby excluding suprathreshold responses and their temporal changes. Thus, a threshold-based pain sensitivity assessment provides a narrow, static, snapshot of the overall pain experience. Furthermore, greater threshold-based sensitivity in women is not unique to pain, but is merely one example of multisensory sex differences where some women show greater detection sensitivity than men to many sensory modalities [4,14]. Therefore, we posit that assessment of pain sensitivity must include both threshold and suprathreshold measures, as well as temporal measures, such as adaptation and habituation. Furthermore, often overlooked is that there are many equally debilitating chronic pain conditions that have a male predominance [5,7,19,29]. Thus, clearly the effect of sex on pain should not be generalized as it is complex, and may depend on a variety of individual and disease co-factors.

In summary, the evidence to date suggests a dichotomy of sex difference findings that depend on the nature of the experimental paradigm. In general, women often show lower pain thresholds and experience greater temporal summation of pain to brief, repeated, or dynamic stimuli than men. However, women also show greater adaptation to sustained longer stimuli and habituation to repeated long stimuli. These seemingly divergent findings could represent two mechanisms: a “sensing response” tied to peripheral and ascending nociceptive pathways, and a “modulation/coping response” resulting from the descending modulation pathways and top-down controls (Fig. 2). We propose that pain sensitivity comprises elements from both the sensing and the modulation/coping systems. We recommend that future studies of the concept of pain “sensitivity” and sex differences interpret their findings within this conceptual framework.

Conflict of interest statement

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References