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Sex Differences in the Neural Representation of Pain Unpleasantness

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Abstract: **Sex differences in pain perception are still poorly understood, but they may be related to the way the brains of men and women respond to the affective dimensions of pain. Using a matched pain intensity paradigm, where pain intensity was kept constant across participants but pain unpleasantness was left free to vary among participants, we studied the relationship between pain unpleasantness and pain-evoked brain activity in healthy men and women separately. Experimental pain was provoked using transcutaneous electrical stimulation of the sural nerve while pain-related brain activity was measured using somatosensory-evoked brain potentials with source localization. Cardiac responses to pain were also measured using electrocardiac recordings. Results revealed that subjective pain unpleasantness was strongly associated with increased perigenual anterior cingulate cortex activity in women, whereas it was strongly associated with decreased ventromedial prefrontal cortex activity in men. Only ventromedial prefrontal cortex deactivations in men were additionally associated with increased autonomic cardiac arousal. These results suggest that in order to deal with pain's objectionable properties, men preferentially deactivate prefrontal suppression regions, leading to the mobilization of threat-control circuits, whereas women recruit well-known emotion-processing areas of the brain.**

Perspective: ***This article presents neuroimaging findings demonstrating that subjective pain unpleasantness ratings are associated with different pain-evoked brain responses in men and women, which has potentially important implications regarding sex differences in the risk of developing chronic pain.***

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Key words: *Sex differences, pain unpleasantness, brain, somatosensory-evoked brain potential, source localization.*

Women are more likely than men to face a variety of recurrent pains, report more severe pain, and feel pain across a greater number of body areas.[30,39] The underlying mechanisms of these differences remain poorly understood and may be caused by any number of sensory and processing variations from the skin to the brain. Very few studies, however, have explored sex differences in pain-evoked brain activity. Those that have, have differed widely in the type of pain stimulus used, neuroimaging technique adopted, and strength of stimulation applied.[5,16,24-26,32,36,49] This makes drawing strong conclusions very difficult. Nevertheless, one promising approach to the investigation of sex differences in brain activation to pain has been to equate pain experiences across the sexes. Doing so helps ensure that any cerebral activation difference obtained between men and women actually reflects a fundamental difference in the way men and women process pain and

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not merely a difference in how pain is initially experienced. To our knowledge, only 2 studies have used a matched-perception paradigm to study sex differences in cerebral activation during the experience of pain. These 2 studies, 1 conducted by Derbyshire et al[16] and 1 by Straube et al,[49] found that compared to men, women show greater pain-evoked perigenual anterior cingulate cortex (pgACC) activation. (In Straube et al, this activity extended into the medial portion of the prefrontal cortex.) The pgACC receives substantial direct input from the hypothalamus and amygdala[4,16,19] and participates in the ongoing evaluation of emotional experiences.[55] As pointed out by Derbyshire et al,[16] this information suggests that for women, the organization of affective responses to pain may be dominated by cingulate circuits. For men, it is not yet clear what may be expected, given the lack of consistent neuroimaging results and the lack of studies that have tested for sex differences in the neural representation of pain affect.

To explore this issue, we used a matched pain perception paradigm where subjective pain intensity was equated across participants but subjective pain unpleasantness (ie, the immediate, disagreeable dimension of pain) was left free to vary among participants. Pain was provoked using transcutaneous electrical sural nerve stimulation while cerebral responses to pain were measured using somatosensory-evoked brain potentials (SEPs) with source localization. In our main analysis, pain-evoked brain activity was correlated to pain unpleasantness separately for men and women. Correlation maps were then compared between the sexes. Women, but not men, were expected to show a significant, positive relationship between pain unpleasantness and pgACC activity. No a priori hypothesis was formulated to describe the relationship between pain unpleasantness and brain activity in men, as the literature concerning effects in men does not favor the formulation of an explicit hypothesis. As an additional, exploratory step, we simultaneously measured autonomic cardiac responses to pain. This additional step appeared necessary to us because previous research has shown that cardiac responses to pain covary with subjective pain unpleasantness in men but not women,[51] thus raising the possibility that sex differences in affective pain regulation and cardiac reactivity to pain share a common neurocircuitry.

Methods

Participants

Eleven healthy men and 13 healthy women, without history of self-reported chronic pain, psychological disorders, or any other diseases, participated in this study after giving their written, informed consent. Medical history was assessed using an in-house health questionnaire. Men and women did not differ in terms of age (men: mean age = 26.1, standard error = 1.9; women: mean age = 23.7, standard error = .7; $t = 1.26$, $P = .22$). The research protocol was approved by the ethics committee of the Centre Hospitalier Universitaire de Sherbrooke.

Subjective Ratings

Verbal numerical rating scales (NRSs) were used to evaluate the intensity of all somesthetic sensations. An innocuous NRS was used to evaluate nonpainful sensations and ranged from 0 to 100, where 0 was defined as "no sensation" and 100 was defined as "extremely intense, but not painful." A noxious NRS was used to evaluate painful sensations and also ranged from 0 to 100, but this time, 0 was defined as "no pain" and 100 was defined as "intolerable pain intensity." In order to distinguish between the scales, participants had to precede all innocuous evaluations by the word *nonpainful*. Using separate 0 to 100 scales to assess nonpainful and painful sensations, respectively, was preferred to the use of a single 0 to 200 scale (where 100 would have represented the pain perception threshold) because it was feared that a single 0 to 200 scale might have been less intuitively used by participants and thus might have led to important evaluation errors.

Pain unpleasantness was also evaluated using a 0 to 100 NRS. This time, 0 was defined as "pain not unpleasant" and 100 was defined as "intolerable pain unpleasantness." Pain unpleasantness ratings were never obtained for innocuous sensations.

Sural Nerve Stimulations

Both nonpainful and painful sensations were provoked using transcutaneous electrical stimulations of the right sural nerve. The sural nerve was stimulated over its retromalleolar path. Stimulations consisted of a volley of 10 electrical pulses (square waves, each 1 ms long) administered at a rate of 320 Hz using a constant current stimulator. A stimulation volley lasted 31 ms. Stimulations were provided using a pseudo-random interstimulus interval of 6 to 12 seconds (geometrical distribution with a mean of 7.4 stimuli per minute). The use of a jittered design allowed us to control for pain-expectation effects, which are known to influence subjective pain reports.[11] Stimulations were provided in 2 separate testing blocks (with an interblock interval of 5 minutes). The first block contained 33 stimuli provided at a stimulation intensity level necessary to provoke strong tactile (but nonpainful) sensations and corresponding to a score of 50 on the innocuous NRS. The second testing block also contained 33 stimuli, but this time, the intensity level was adjusted to ensure the subjective experience of mild pain—corresponding to a score of 15 on the noxious NRS. Mild pain was targeted because sural nerve sensations are typically experienced as more unpleasant than intense by participants. As a result, high levels of targeted pain intensity run the risk of causing extremely high levels of pain unpleasantness and thus elevated drop-out rates. Stimulation intensity always remained constant within blocks. Each testing block lasted 4.5 minutes. The nonpainful testing block was always presented before the painful testing block. This is important because painful testing blocks can potentially produce spinal sensitizing effects that can carry over and affect the evaluation of all subsequent blocks. The use of an incremental testing design,

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