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Sex differences in perceived pain are affected by an anxious brain

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ABSTRACT

Decades of research confirm that women have greater pain sensitivity than men. Women also show greater overall anxiety sensitivity than men. Given these differences, we hypothesized that sex differences in anxiety would explain sex differences in experienced pain and physiological responses to pain (at both spinal and cortical levels). By measuring subjective pain, state/trait anxiety, nociceptive flexion reflexes, and somatosensory evoked potentials (SEPs), it was possible to test the effects of anxiety on the processing of painful drives at different levels of the neuraxis while also documenting the role played by anxiety on sex differences in experienced pain. Results confirm that women are indeed more sensitive to pain than men. Importantly, this difference was accompanied by a significant sex difference in cortical activity (SEP amplitude) but not spinal nociceptive activity, suggesting that much of the sex difference in experienced pain is attributable to variations in thalamocortical processing and to ensuing changes in the appraisal of and/or emotional response to noxious insult. In support of this claim, we found that sex differences in cortical activity and subjective pain disappeared when trait anxiety was controlled for. This means that stable predispositions to respond with heightened apprehension contribute to baseline pain sensitivity differences between the sexes. These results indicate that the modulatory effect of affect on pain-related brain processes may explain why men and women experience painful shocks so differently. In our study, the mediating role of anxiety on sex differences in pain was tested and confirmed using path analysis.

1. Introduction

Sex differences in perceived pain have been widely investigated over the last few years, and experimental studies on this issue overwhelmingly indicate that women experience pain as more intense than men do [11,17,42,43]. Interestingly, women also show greater overall anxiety sensitivity than men, resulting in greater catastrophic cognitions, greater baseline physiological arousal, and the endorsement of greater anxiety symptoms [54]. Given this sex-related difference in anxiety sensitivity, a growing number of studies have begun to investigate how anxiety affects the processing of painful stimuli in men and women [9,15,21,25,30,41,45]. The picture beginning to emerge from nearly a decade of work on this issue is that anxiety responses to pain contribute significantly to the pain sensitivity difference observed between men and women [21,25,44].

One possible explanation for the moderating effect of anxiety on sex differences in perceived pain is that increased anxiety facilitates the mobilization of resources required for the detection of actual or potential harm, ultimately exacerbating the experience of pain (see Rollman et al. [46] as well as Henderson et al. [20] for a similar argument). Although plausible, this explanation remains hypothetical and does not specify how anxiety interacts with biological sex to affect perceived pain. Thus we currently ignore whether anxiety affects perceived pain because it sensitizes spinal and/or supraspinal nociceptive processing systems or because it changes the way pain is appraised.

Interestingly, neuroimaging studies concerned with explaining sex differences in perceived pain reveal that when exposed to a standardized painful stimulus, women show greater cortical activity than men in the midcingulate cortex [20], the prefrontal cortex, the insula, and the thalamus [36]. This means that women show increased activity across brain regions targeted by the medial pain pathway. Because this pathway is thought to code for affective/motivational components of the pain experience [1,39,40], increased activity here would agree with the idea that sex differences in perceived pain are attributable to an affective (state-sensitive) recoding of afferent signal strength.

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Alternatively, the moderating role of anxiety on sex differences in pain may be related to a sensitizing effect of anxiety on spinal pain processing systems. This would be consistent with studies that show lower spinal withdrawal reflex thresholds and higher subjective pain in women than men [13,34,50]. It is important to point out, however, that anxiety is a multifaceted concept, describing both transient reactions to threat (state anxiety) and a stable predisposition to respond with heightened apprehension (trait anxiety; see Spielberger et al. [53]). Thus, depending on the type of anxiety investigated, results detailing the link between sex and pain may vary widely. To our knowledge, no study has yet investigated both state and trait anxiety when exploring the neurophysiological underpinnings of the sex difference in pain. Our objective, therefore, was to study the impact of anxiety on sex differences in pain by measuring pain (self-ratings), state/trait anxiety, nociceptive flexion reflexes (NFRs), and somatosensory evoked potentials (SEPs) in both men and women.

2. Methods

2.1. Subjects

Twenty-nine healthy adults, including 14 men (24.8 ± 3.9 years old) and 15 women (23.7 ± 2.2 years old), participated in this study. None suffered from chronic pain, cardiac, or respiratory problems. The protocol was approved by the ethics committee of Centre Hospitalier Universitaire de Sherbrooke.

2.2. State and trait anxiety

The State-Trait Anxiety Inventory (STAI) was used to measure anxiety. The STAI consists of two 20-item questionnaires scored using a 4-point Likert scale. It is considered a standard index of situational (state, STAI-S) and dispositional (trait, STAI-T) anxiety. Psychometric properties for the STAI are excellent [2,53], and the instrument is frequently used in experimental pain research [14,16,33,51].

2.3. Pain ratings

Numerical rating scales were used to evaluate the intensity of both innocuous and noxious sensations. The innocuous scale ranged from 0 to 100, where 0 was defined as no sensation and 100 was defined as extremely intense, but not painful. The noxious scale also ranged from 0 to 100, but this time 0 was defined as no pain and 100 was defined as the most intense pain imaginable. To distinguish between the scales, participants had to precede all innocuous evaluations by the word nonpainful.

2.4. Sural nerve stimulations

In this study, both nonpainful and painful sensations were evoked through transcutaneous electrical stimulations of the sural nerve. The sural nerve was stimulated over its retromalleolar path at a fixed frequency of 0.14 Hz (ie, once every 7 seconds). Stimulations consisted of a volley of 5 electrical pulses (square waves, each 1 ms long) administered at a rate of 240 Hz using a constant current stimulator. A stimulation volley lasted only 21 ms. Past studies confirm that a withdrawal reflex response can be triggered when stimulation currents are strong enough to recruit Aδ fibers [47]. This means that the withdrawal reflex response can be used to chart spinal nociceptive responding specifically. Reflex responses were measured via an electromyographic (EMG) recording of the biceps femoris. Reflex threshold was determined using an iterative staircase method [60]. EMG activity was considered reflexive when its amplitude exceeded baseline activity levels by at least 1.5 standard deviations. Withdrawal reflex activity was quantified by calculating the integral of the rectified EMG signal between 90 and 150 ms poststimulation. Stimulations were provided in separate testing blocks that became incrementally more intense (interblock interval of 5 minutes). Stimulation intensity, however, remained constant within blocks. Blocks contained 22 shocks provided at each of the following intensity levels: 50% below reflex threshold, at reflex threshold, and 30% above threshold. It is important to point out that we used an incremental as opposed to a random presentation design because pilot testing confirmed that our most intense testing block (ie, 30% above threshold) produced spinal sensitizing effects that could carry over and affect the data obtained on subsequent blocks. This sensitizing effect was only seen at the highest stimulation intensity level. An incremental testing design, therefore, prevented potential carryover effects from the most intense block to both other blocks.

2.5. Somatosensory-evoked brain potentials

SEPs were time-locked to each sural nerve stimulation and were obtained at the vertex (Cz) using a monopolar montage with a right-ear reference. Using a Powerlab system (ADInstruments), our signal was sampled at 200 Hz and filtered online within a 0.5- to 30-Hz band pass. Electro-oculographic activity was also recorded, and SEP trials contaminated by electro-oculographic artifacts (±60 μV) were eliminated from the analyses. This resulted in less than 5% loss of trials. SEPs were baseline corrected between 0 and 100 ms prior to stimulation onset, and averaged across trials. This was done separately for each of our 3 testing blocks. From the average waveforms, specific epochs were isolated to capture both early (P45, N100) and late (N150, P260) somatosensory components. P45 activity was examined in the 45- to 5-ms poststimulus interval, whereas N100 activity was examined in the 90- to 120-ms interval. N150 activity was examined in the 135- to 150-ms interval, and P260 activity was examined in the 230- to 350-ms interval, consistent with previous publications demonstrating that these epochs constitute stable periods during which scalp voltage topography is invariable and during which the configuration of current sources remains constant [4–6,8]. SEP amplitudes were quantified by determining the local voltage maximum obtained in each of the time intervals described above (ie, peak detection method). This approach was favored over a mean amplitude technique because in our study participants were exposed to progressively more intense stimulations as testing advanced. This means that progressively slower conducting fibers were recruited as participants progressed from block to block, consistent with the slower conduction velocity of nociceptive as opposed to nonnociceptive afferents. The result of such a progressive change in conduction velocity between blocks is an overall increase in the interblock variability of peak amplitude latency (a phenomenon known as latency jitter). Between-block jitter was confirmed in our data because the latency of the peak P260 waveform (ie, the latest and arguably most jitter-sensitive component) increased significantly when testing progressed from threshold to our most intense block (passing from a peak latency of 237.1 ± 3.5 ms to a peak latency of 241.3 ± 4.6 ms, $P < .05$). Within-block variability was also present and increased progressively as a function of block strength ($r = .81$, $P < .05$). This means that a significant amount of within-block jitter was also present, especially when stimulation intensity was strong. The result of all this jitter is: (1) a smeared or reduced peak amplitude obtained on average SEP waveforms, and (2) a decreased likelihood of finding condition (or in our case block) effects when the mean amplitude technique is used to quantify voltage strength. To offset this potential bias, and ensure the capture of legitimate interblock differences in SEP amplitude,