



# PAIN

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### Gender, Pain, and the Brain

Around 15 years ago, there was a handful of imaging papers examining brain responses to somatic noxious stimulation.<sup>1-5</sup> Those papers demonstrated that delivering a noxious stimulus results in the activation of many brain structures including the thalamus, basal ganglia, cerebellum, and the insular, primary sensory, secondary sensory, anterior cingulate, and prefrontal cortices. Since then there has been an exponential rise in the number of functional imaging studies using noxious stimulation.<sup>6,7</sup> A Medline search using the terms “functional imaging or PET or fMRI” and “pain” yields 1,131 hits. Surprisingly, however, adding the term “gender or sex” yields just 30 hits. The relevant papers from those 30 are summarized in Table I.

At first glance, the dearth of imaging studies examining pain and gender is difficult to understand. It is well known and well documented that many clinical pain disorders disproportionately affect women. In her seminal review of 1998, Karen Berkley documented that almost half of the 78 clinical pain disorders reviewed had a female bias, whereas just under a third had a male bias.<sup>8</sup> Furthermore, meta-analysis of studies with experimental noxious stimuli has generally revealed women to be more “pain sensitive”; that is, women respond more readily with pain to a stimulus that men may report as not painful, and women report more pain to stimuli that both sexes find painful.<sup>9</sup> From there it is a fairly trivial deduction that women may experience more clinical pain because of their greater pain sensitivity and that this sensitivity might be caused by different neuropsychological responses to sensory stimulation.

Unfortunately, although formulating this deduction is trivial, the details are vastly more complex. A dizzying myriad of factors can influence pain, which is one reason the biopsychosocial model of pain is generally accepted.<sup>10,11</sup> The biopsychosocial approach to pain is based on several propositions, the central one being that an individual's emotions and behavioral activity in response to an event are influenced by his or her appraisal of that event and environmental circumstances. In addition to the biology of a noxious event, the biopsychosocial model introduces psychological and social factors that may mitigate or increase the final experience of pain. Thus, a given stimulus might be experienced as more or less painful because of hormonal fluctuation, criterion effects, differences in body size, skin thickness, blood pressure, social expectations, cognitive variation, method of stimulation, and differences in psychological traits such as anxiety and depression. Given the many varied sources of variation, it is perhaps unsurprising that gender differences in response to noxious stimulation are generally small and are swamped by the variation between individuals. Berkley summarized the field thus: “For experimentally delivered somatic stimuli, females have lower thresholds, greater ability to discriminate, higher pain ratings, and less tolerance of noxious stimuli than males. These differences, however, are small, exist only

### UPCOMING ISSUES

**What Does Pain Hurt?**

**Fibromyalgia**

**Pelvic Pain**

**Table I**  
Results from pain-imaging studies reporting gender differences

Study	Amygdala	Thalamus	Insula	ACC	S1	S2	PFC
Paulson et al. <sup>12</sup> (contact heat)		F↑	F↑				F↑ M↑
Derbyshire et al. <sup>13</sup> (laser)			M↑	F↑		M↑	M↑
Moulton et al. <sup>18</sup> (contact heat)				M↑	M↑ F↓		M↑ F↓
Berman et al. <sup>14</sup> (rectal distension)			M↑				
Kern et al. <sup>15</sup> (rectal distension)			F↑	F↑	M↑		F↑
Naliboff et al. <sup>16</sup> (rectal distension)	F↑		M↑	F↑			M↑ F↑
Berman et al. <sup>17</sup> (rectal distension)	F↓		M↑	F↓			
Zubieta et al. <sup>26</sup> (opioid binding)	M↑	M↑					
Smith et al. <sup>27</sup> (opioid binding)	M↑	M↑					

*Notes:* Greater (↑) or reduced (↓) activation or opioid binding in men compared with women is indicated with “M” and in women compared with men with “F.” A blank indicates that no significant between gender differences were found or assessed in that region for that study. Where “M” and “F” are both in the same cell, mixed gender responses in subregions or on opposite sides were reported. ACC = anterior cingulate cortex; S1 = primary sensory cortex; S2 = secondary sensory cortex; PFC = prefrontal cortex.

for certain forms of stimulation and are affected by many situational variables.”

One would have to be a considerable optimist to expect functional imaging to provide clarity under the circumstances described, which might, in part, explain the dearth of imaging studies examining pain and gender. The studies that have been completed provide mixed results. In 1998, Paulson and colleagues demonstrated greater responses in the anterior insula and thalamus in female subjects and showed prefrontal activation in the right hemisphere in male subjects and in the left hemisphere in female subjects using noxious heat.<sup>12</sup> In 2002, our group reported greater activation of the perigenual and ventral cingulate cortex in female subjects and greater activation of the parietal, secondary sensory, prefrontal, and insular cortices in male subjects using noxious laser stimuli.<sup>13</sup> In 2000, Berman and colleagues reported greater insula activity in male subjects receiving an aversive rectal distension, opposite to the greater female insula activity seen in a later rectal distension study by Kern and colleagues.<sup>14,15</sup> Naliboff et al. and Berman et al. also noted increased insula activation in males when using a nonpainful but uncomfortable rectal distension.<sup>16,17</sup> Recently, Moulton and colleagues demonstrated reduced activation in the primary sensory, anterior cingulate, and prefrontal cortices during noxious heat in females compared to males<sup>18</sup>—a result that differs from those of both Derbyshire and colleagues<sup>13</sup> and Paulson and colleagues.<sup>12</sup> The results of these studies are summarized in Table I.

Such variability is not surprising because both gender and sensory experience are complex. In 1637, Descartes reported an experiment in which he scraped the tissue from the back of an ox’s eye and placed the eye in a shutter, allowing light to enter the front of the eye.<sup>19</sup> Descartes reported that he saw an inverted and reversed image on a sheet of thin paper placed where the retina would have been in the living animal, demonstrating that the eye was a kind of camera obscura. Thus, Descartes demonstrated the mechanical or physical beginnings of vision, but because we do not see an upside-down world, he rejected vision as merely the result of physical action in the eye

and brain. In the *Second Meditation*, Descartes explains that “perception is neither an act of vision, nor of touch ... but only an intuition of the mind.”<sup>20</sup> The orderly and calculable penetration of light rays through the camera obscura exposes the light to the reason of the mind, but sensation does not dazzle or drown the mind. Human beings are self-located within sensory experience, but we are not immersed in it; our intuition of ourselves as particular beings with particular location and experience is opened by, rather than collapsed into, our senses. Rather than reflexively responding to physical information, we exercise judgment, and so our experience can change according to our judgment. Physical information can be static, while the experience or meaning that we extract changes. An excellent demonstration of this phenomenon is provided via sine-wave speech.<sup>21</sup> When we first hear a sine-wave sentence, it sounds like whistling and squeaking, but after we hear the sentence in normal speech the sine-wave version becomes intelligible (demonstrations are available at [www.mrc-cbu.cam.ac.uk/~mattd/sine-wave-speech](http://www.mrc-cbu.cam.ac.uk/~mattd/sine-wave-speech)). The physical information remains the same, but our judgment, our brain activity, and what we experience change. Any systematic gender differences in subjectivity, therefore, are liable to change sensory experience, including pain.

Systematic differences might be expected because gender is not just one more idiosyncratic difference but is a cultural construction, on top of biological facts, with considerable coherence and universal recognition. Consistent gender differences in brain activation when processing physically noxious information are highly probable, but finding those differences could require a very large sample of volunteers to cut through the variation getting in the way. Studying large samples with functional MRI or other imaging techniques, however, is costly, time consuming, and not always professionally beneficial. A more profitable approach could involve the manipulation of noxious or potentially noxious stimuli, to produce different pain experiences in men and women, that extends beyond the simple manipulation of stimulus intensity. Examples include the manipulation of offset analgesia or stimulus adaptation,

which leads to surprising alterations in pain experience despite delivery of consistent noxious energy.<sup>22</sup> These alterations in experience are believed to follow alterations in descending inhibition dependent upon subjective factors that presumably vary across gender and could be profitably investigated.

It is important to consider new experimental approaches because it is not obvious that gender differences in threshold have any clinical significance. Although women generally respond to noxious stimulation with a greater report of pain than men, the difference is small. In contrast, women suffer a disproportionately greater number of pain disorders and dominate those pain disorders by a large margin relative to men. Although a link from increased pain sensitivity in women to the increased prevalence of pain disorders in women is plausible, the relatively small difference in pain sensitivity makes that link improbable.

It is more plausible that separate mechanisms drive the slightly increased pain sensitivity in women and the female dominance of clinical pain disorders. In her paper, Berkley describes three potential sources of gender difference that might explain the disproportionate presence of females suffering clinical pain disorders. First, there is the vaginal canal, which provides an entrance for pathological agents. Second, there is the temporal, cyclical variation in sex hormones that is unique to women, and third, there is the difference in concentration of the sex hormones (estradiol, progesterone, and testosterone) in men and women. I would add to this list the continued cultural separation of men and women that is bound to influence experience in general and may also influence pain experience specifically.

The role of sex hormones in facilitating pain has been investigated for some time. Animal studies have shown, for example, greater opioid-mediated stress-induced analgesia in male rats compared with female rats.<sup>23,24</sup> Estrogen is believed to cause this difference by suppressing stress-induced analgesia.<sup>25</sup> More recently, Zubieta and colleagues have demonstrated increased mu-opioid binding, implying less endogenous opioid binding, during pain in the anterior thalamus, ventral basal ganglia, and amygdala in women compared with men.<sup>26</sup> A similar study also demonstrated reduced endogenous opioid activation in the thalamus, nucleus accumbens, and amygdala in women during the low-estrogen period of their menstrual cycle.<sup>27</sup>

Similar to the brain activation studies, hormone studies are beset by inconsistencies and confusions. If estrogen suppresses opioid-mediated stress-induced analgesia, it might be expected that endogenous opioid activity would be highest during the low-estrogen phase of the menstrual cycle. Smith and colleagues report the opposite. Nevertheless, the evidence that men and women differ in their opioid responses to acute pain is supported by the finding that women respond to the kappa-opioid agonist pentazocine with significantly greater analgesia than men.<sup>28</sup> Recently it has been suggested that at least some forms of chronic pain might also be linked to changes in endogenous opioid activity.<sup>29</sup> This research has not yet, however, been extended to consider gender, so the work on opioid activity and gender remains restricted to acute pain models that can only be applied cautiously to chronic pain syndromes.

Although biological differences are plausible to explain

gender differences in pain experience, there are also psychological and cultural factors to consider. The social roles of men and women may not be as clearly defined as they once were, but women still carry most of the domestic responsibilities within the family, and if they work as well as have a family, women are more likely to experience conflict and take on a substantially greater share of the total household workload.<sup>30</sup> It is not clear how such differences might lead to the development or worsening of a pain disorder, but when people feel overwhelmed by their commitments, they are at risk from depression and other detrimental mood changes that can heighten somatic experience. Over half of clinically depressed patients also report pain, but even mild symptoms of depression are associated with twice the normal level of chronic painful conditions.<sup>31</sup>

In addition, several authors have linked the rise of a patient-centered approach and the growing popularity of a social model of health and disease with increases in patients reporting ill health without clear objective markers of disease.<sup>32-34</sup> These claims of ill health may originate from psychosocial problems, involving a fractured personal identity, and feelings of displacement, estrangement, or meaninglessness that can be difficult to articulate but that might find a ready explanation in a medically endorsed chronic illness. Somatic symptoms, readily experienced by people who are nevertheless healthy,<sup>34</sup> can be diagnosed or judged as a medical problem and thus provide meaning for psychosocial distress. Women may be more at risk from such diagnosis because of a more vulnerable cultural position that places them in conflicting social roles and makes them more likely to visit the doctor both for their own health and that of their children.<sup>10,30</sup> Investigating these cultural and subjective factors provides a methodological difficulty because they are challenging to quantify. Changes in cultural roles, ill health, and emotionality have a deeply subjective character that cannot be easily demonstrated empirically. How to translate these factors into an imaging study is far from obvious, and the very effort might be nonsensical. There are some levels of analysis that do not track easily onto one another.

Clearly men and women are not the same, and the ways in which we are different probably affect our experience of pain. Simple differences in body size and skin thickness might account for different pain experience in response to the same physical stimulus. At a greater level of complexity, different neuronal organization and opioid receptor density might account for differences in pain sensitivity. Whether and how these differences explain the higher incidence of clinical pain disorders in females remains very much an open question. More and larger studies provide one obvious way forward. There are, however, opportunities for targeted investigations of endogenous analgesic and brain mechanisms underlying gender differences. A myriad of other factors, including psychological and cultural differences, are also likely to influence gender difference in the experience and expression of pain disorders. Examining these factors using modern imaging procedures might be obvious and relevant sometimes, but not at all obvious and with uncertain relevance at other times. Deciding how to integrate all the various factors that can influence pain and gender with the technology available remains a considerable challenge.

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