OPINION

Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon

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Abstract | A clear majority of patients with chronic pain are women; however, it has been surprisingly difficult to determine whether this sex bias corresponds to actual sex differences in pain sensitivity. A survey of the currently available epidemiological and laboratory data indicates that the evidence for clinical and experimental sex differences in pain is overwhelming. Various explanations for this phenomenon have been given, ranging from experiential and sociocultural differences in pain experience between men and women to hormonally and genetically driven sex differences in brain neurochemistry.

Chronic pain is the most prevalent human health problem, affecting over one-quarter of the world's population, and is rising in incidence as the population ages[1]. Women are greatly overrepresented among patients with chronic pain[2–4]. A number of common chronic pain syndromes can only occur in women (including endometriosis, vulvodynia and menstrual pain). Furthermore, some highly prevalent chronic pain syndromes that are found in both sexes (including chronic fatigue syndrome, fibromyalgia, interstitial cystitis and temporomandibular disorder) occur overwhelmingly more often (in more than 80% of cases in which treatment is sought) in women. Last, the chronic pain syndromes with the highest prevalence overall — headache, migraine, low back pain, neck pain and knee pain (mostly osteoarthritis) — all have marked female predominance. (FIG. 1 shows estimates of excess female prevalence in large epidemiological studies of pain[5]). There are, of course, male-specific (chronic prostatitis), male-dominated (gout) and male-prevalent (cluster headache) pain states, but these tend to be less prevalent overall.

Although the underlying reasons for the sex bias observed in pain are still hotly debated, the fact that clinical pain is more prevalent in women is well beyond doubt. This epidemiological reality, however, has been and continues to be largely ignored by the pain research community. Many jurisdictions now insist that clinical studies are performed on both sexes, but no such mandate exists for preclinical research. A recent literature search demonstrated male bias in experimental subject choice in eight out of ten biological disciplines[6], and a huge male-orientated bias can also be observed in the preclinical pain literature[7] (FIG. 2). Although much more attention has been paid to the topic of sex and/or gender differences in pain in the past few decades[5] (and sex differences in neuroscience more generally[8]), there is little evidence to suggest that female mice and rats are becoming more popular as research subjects overall. The omission of female animals from preclinical experiments can have serious implications, as some sex differences are qualitative rather than quantitative, and failure to appreciate them can lead to either missing biological phenomena entirely or overgeneralization of findings (BOX 1).

The aims of this article are to re-evaluate the evidence indicating that women are more sensitive to pain than men, to examine factors that complicate strong conclusions as to the nature of this sex difference and to detail the various underlying mechanisms that have been proposed to explain it. The article will not attempt to comprehensively review the underlying mechanisms, but will attempt to categorize the types of explanations that have been put forward.

Are women more sensitive to pain?

The predominance of females among patients with chronic pain might be explained in one of three non-mutually exclusive ways. First, it is possible that women simply seek out health care services at higher rates than do men and/or are more willing to report pain on surveys than men, and thus will be tallied higher in epidemiological studies of various types. Second, it is possible that women have higher susceptibilities to common chronic pain syndromes than men and thus will be more likely to develop conditions that feature pain as a symptom. Last, it is possible that women have a greater sensitivity to and/or a lower tolerance of pain than men, leading to higher percentages of women crossing the threshold at which experienced pain rises to the level of a diagnosed 'pain syndrome'. In this case, pain levels in pain syndromes experienced by both sexes would be expected to be highest in women. Note that higher pain sensitivity in women might be due to biological sex differences in ascending pain transmission pathways, descending pain modulation pathways and/or any number of psychological phenomena that affect pain. There are also various possible explanations for apparent sex differences in analgesic responsivity (for example, to opioids)[9]; these could be due to differential drug pharmacokinetics or pharmacodynamics or simply to different starting pain levels.

It has been surprisingly difficult to determine which of the three scenarios outlined above provides the most convincing explanation for sex differences in chronic pain prevalence. Women do use health care services at rates exceeding those of men for painful and non-painful disorders alike[10]. There are multiple reports that suggest that pain levels within chronic pain syndromes are markedly higher in women than men, including a recently published

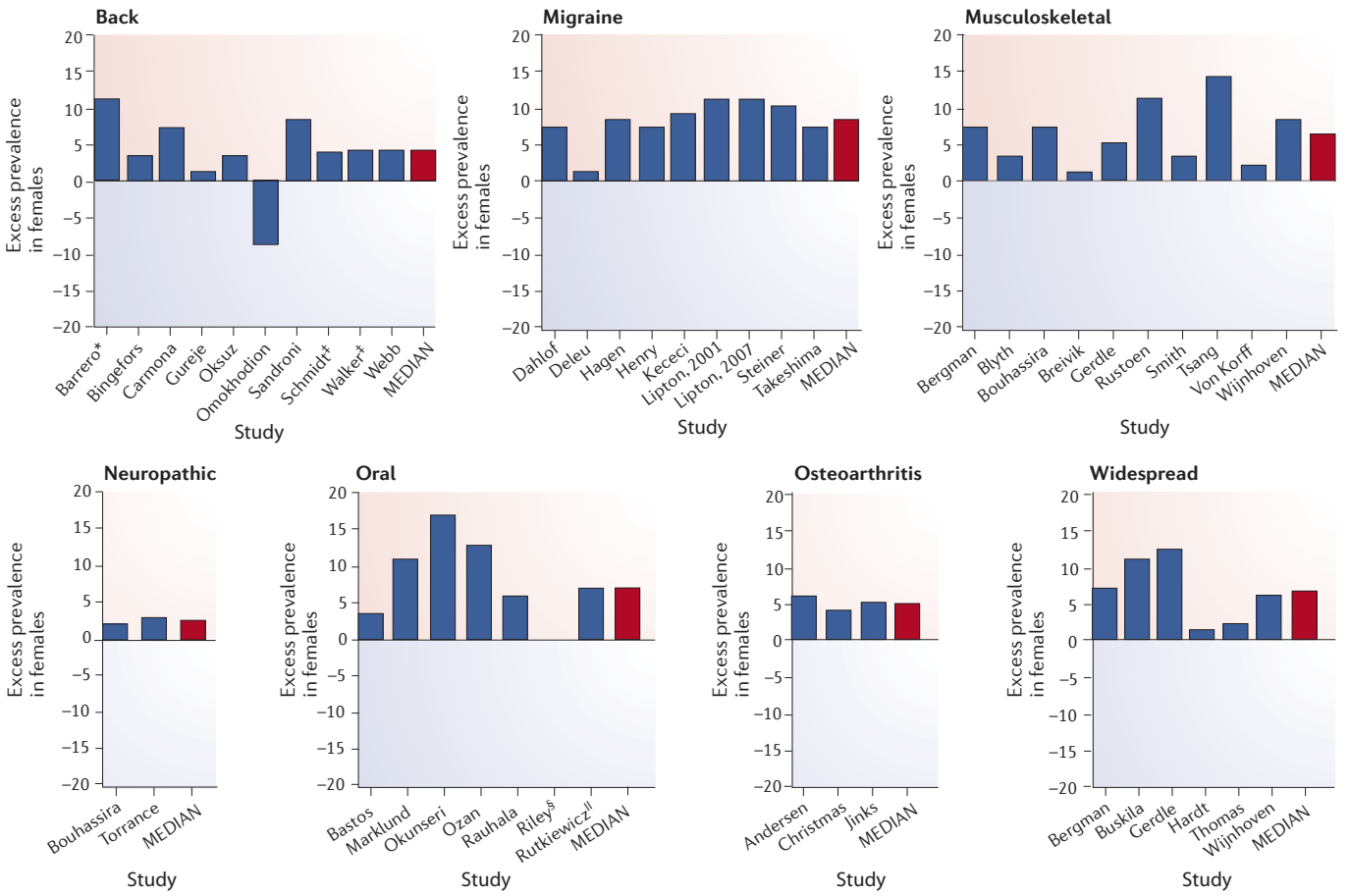


Figure 1 | **Sex differences in prevalence of chronic pain syndromes.** The epidemiological data presented here are taken from REF. 5 but were derived from large, general population-based (self-report) studies conducted via surveys or telephone interviews (see Supplementary information S1 for full citations). Data from clinical studies are not included because of bias associated with the fact that health care services are used more by women than by men. Each blue bar represents the excess prevalence of the pain condition in women reported in a single epidemiological study; the red bar to the right represents the median excess prevalence within the category. The definitions of pain prevalence (including current pain, 1–12-month pain duration or chronic pain) differed widely across the studies, but the definition in each was the same for males and females, and thus sex differences in prevalence can be compared directly. In some cases, the male–female difference scores plotted are averages of multiple prevalence estimates. The average of the category medians is 5.5% excess female prevalence. *Indicates the average of different age ranges. ‡Indicates the average of different durations. §Indicates the average of different numbers of pain-related symptoms. ‖Indicates the average of different pain locations).

review of 11,000 electronic medical records of men and women with the same diagnosis[11]. However, the real test of the hypothesis that pain sensitivity itself is higher in women requires controlled laboratory experimentation.

Laboratory studies of sex differences. Many studies of sex differences in pain sensitivity have been conducted (for recent examples, see REFS 12–14), and many reviews and meta-analyses of these studies exist[5,9,15–19]. As might be expected with a biological domain as heterogeneous as pain, the picture emerging from these studies is complex. Some studies show notable sex differences in pain sensitivity, whereas others do not. A persistent concern is that laboratory studies of pain sensitivity between the sexes are confounded by human subject–experimenter interactions involving gender role expectations, although contradictory data have been generated relating to this issue[5,20]. Overall, sex differences seem to be easier to evince in certain pain modalities than in others (such as in heat or pressure-induced pain compared with ischaemic pain), using certain dependent measures (such as tolerance as opposed to pain intensity or unpleasantness ratings) and at certain time points (such as early rather than late after introduction of the noxious stimulus), and exhibit small-to-moderate effect sizes (see REFS 5,15 for comprehensive recent reviews).

What has struck many researchers, however, is the fact that when differences are observed, they almost unanimously show that women have a higher sensitivity and lower tolerance to pain than men, report higher pain ratings and have a greater ability to discriminate among varying levels of pain. Nonetheless, a true consensus has been hard to reach; a consensus working group published a report in 2007 in which a direct statement that women were more sensitive to pain than men in the laboratory was conspicuously absent[19]. A recent review suggests that the informal consensus that women are more sensitive to pain is actually due to a bias related to participant selection criteria and an overemphasis on pain measures showing sex differences rather than ones that do not[15]. From a re-analysis of the relevant data (BOX 2), I conclude that this critique is too conservative in its definition of what

constitutes a sex difference; the evidence is actually overwhelmingly in support of the contention that women are more sensitive to pain, although the size and importance of this sex difference could be debated.

In addition to sex differences in pain, sex differences in response to opioid analgesics have also been intensely studied. A recent meta-analysis concluded that morphine is moderately more efficacious in women than in men in both clinical (largely patient-controlled analgesia) and experimental studies; however, the picture becomes far less clear for other μ-opioids and especially for mixed μ- and κ-opioid-acting compounds (such as butorphanol, pentazocine and nalbuphine)[9]. In contrast to the animal literature on sex differences in pain[21], which generally supports the informal consensus of higher pain sensitivity in females, the animal literature on sex differences in opioid analgesia reaches a conclusion that dramatically opposes the human situation, with most studies showing increased μ-opioid analgesia in male rodents compared with female animals[22,23]. No explanation of this apparent species difference has been proposed. Of note, the single study examining this issue in non-human primates (*Macaca mulatta*) reported that male monkeys exhibited more analgesia from low-efficacy μ-opioid and κ-opioid agonists than did female animals[24].

Influence of hormones. Determining whether women have different sensitivity to pain or analgesia compared with men is complicated by the hormonal cyclicity of women; the differential sensitivity might only be evinced in certain phases of this cycle. Much attention has been paid to this issue, although the relevant studies have been criticized for various methodological problems[19,25]. Some clinical pain conditions in women vary with the menstrual cycle[25]. A meta-analysis of experimental studies revealed that women have a higher pain threshold and tolerance during the follicular phase (with small-to-moderate effect sizes) in every stimulus modality except electrical pain, in which the highest pain thresholds were associated with the luteal phase[26] (note that studies following the publication of this meta-analysis have produced conflicting results[5,20]). A more recent narrative review that used a different definition of menstrual phases compared with that used in the meta-analysis concluded that increased reactivity to pain occurs peri-menstrually and mid-cycle[27].

Even one of the simpler relevant questions remains a matter of ongoing debate: are oestrogen and progesterone pronociceptive or antinociceptive? There are many extant reports of pain modulation in both directions by gonadectomy, oestradiol or hormone replacement therapy (with or without a progestin). Generally, if effects are seen, gonadectomy increases pain sensitivity, especially for acute pain[28]. By contrast, oestradiol and progesterone given to ovariectomized animals generally cause hypoalgesia[28,29], if effects are observed. Human studies of clinical pain are even more complex, with a multitude of findings in both directions as well as null results. Craft[29] speculates that this complexity may arise from the widespread distribution of oestrogen receptors in pain-relevant loci, possibly biphasic dose–response relationships, methodological inconsistencies and the ignored modulatory influence of other steroids such as testosterone, oestriol and oestrone.

Complicating interactions. The situation is complicated further by findings from animal studies that show robust interactions between sex and other factors in relation to pain sensitivity. The primary factor among these is genotype. Studies in mice[21,30–32] and rats[32–36] have demonstrated that sex differences in pain and analgesia can be demonstrated in certain strains but not others. The effects of gonadal hormones on pain-related traits are similarly strain-dependent[21,37]. Sex–strain interactions undermine the entire concept of sex differences in that they (at least partially) moot the question: which sex is more sensitive to pain? A more sophisticated perspective is that sex and genetic background (and their interaction) are both simply components of inter-individual variability that need to be explained. As might be expected given this interaction, genes (quantitative trait loci) with sex-dependent effects on pain trait variability have been uncovered[38–42]. A recent study uncovered a three-way interaction in both mice and humans between sex, genetics (*AVPR1A* genotype (*AVPR1A* encodes the vasopressin 1A receptor)) and acute stress[43].

Recent mouse studies have revealed another surprising factor that interacts with sex to modulate pain: social interaction. In these studies, mice were placed in observational apparatuses in which some of the animals were in pain (which was induced by intraperitoneal injection of acetic acid) and some were not, and both mouse location and pain behaviour were measured. Unaffected female but not male mice approached cage mates (but not strangers) that were in pain and spent excess time in physical proximity to their hurting familiar[44]. This social approach appears to be an effective analgesic, as a negative correlation was obtained between contact time and pain behaviour[44]. Social interaction can also affect pain behaviour in male mice. When mice were tested in a dyad in which only one was injected with acetic acid, either stress-induced analgesia or stress-induced hyperalgesia was observed, depending on the threat level dictated by facets of the testing situation[45]; these effects are only seen in unfamiliar male mice.

Last, in rodents, sex has been shown to interact with prenatal or neonatal inflammation[46,47] and/or prenatal or neonatal stress[48–51] to affect pain sensitivity in adulthood.

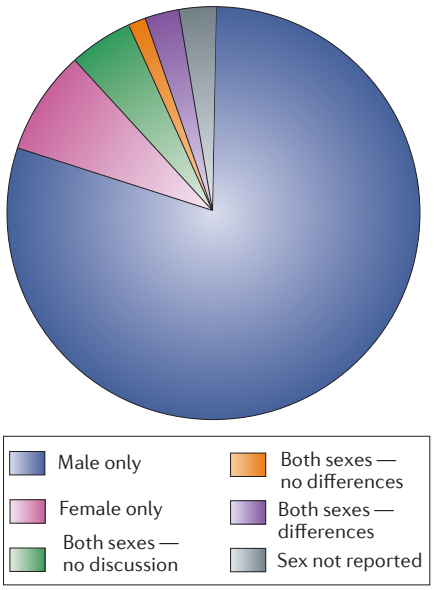


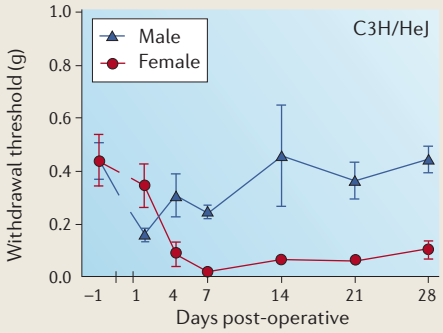
Figure 2 | **Subject choice and reporting practices in preclinical studies of pain.** Data are from a survey of papers published between 1996 and 2005 reporting awake, behaving non-human animal pain experiments[7]. Seventy-nine percent of those experiments used male rodents only. Of studies using both sexes, most featured no discussion of whether sex differences were observed or not. In 3% of studies, the animals' sex was not even reported. No convincing trends in subject characteristics were observed within this 10-year period in any category (not shown).

Potential underlying mechanisms

Although, as outlined above, the debate over the existence of sex differences in pain is not yet over, some researchers have turned their full attention to the task of uncovering mechanisms underlying such differences. There are three operationally defined types

Box 1 | **Male-specificity of the involvement of spinal Toll-like receptor 4 in pain**

Interest in the importance of cells of the immune system in chronic pain biology has been growing among pain researchers. Indeed, spinal cord glia are now thought to be intrinsically involved in the cell-to-cell signalling pathways that produce chronic pain[99,100]. Toll-like receptors (TLRs) are receptors that initiate an immune response[101]. In the CNS, TLR4 is expressed primarily by microglia[102] and is solely responsible for the biological activities of the endotoxin lipopolysaccharide (LPS)[103]. TLR4 is thought to have a broad role in pain as TLR4 loss-of-function mutant mice have reduced allodynia and/or hyperalgesia following transection of the L5 spinal nerve[104] or chronic constriction injury of the sciatic nerve[105]. However, in C3H/HeJ mice with a dominant-negative mutation of the *Tlr4* gene (rendering TLR4 dysfunctional in this strain), only the males displayed reduced allodynia after nerve injury (as was previously reported in REF. 104); female C3H/HeJ mutant mice displayed normally robust allodynic responses (see the figure; data are from REF. 53). Symbols represent mean ± standard error of the mean von Frey fibre withdrawal thresholds before and after spared nerve injury. Further experiments using a selective agonist (LPS) and antagonist (LPS from *Rhodobacter sphaeroides*) of TLR4 revealed no apparent involvement of spinal TLR4 in pain processing in female mice[53]. Why was this not already known? A PubMed search conducted on 11 February 2012 using the search terms 'glia AND pain AND (mouse OR rat)' yielded 529 hits. However, of the accessible, English-language papers in the primary literature featuring behavioural measures, only four tested both sexes of mice. Analgesic development of any TLR4 antagonist must take this sex difference into account if it is to succeed.



of sex differences: sexual dimorphism, in which some end point exists in only one sex (nursing behaviour, for example), or in two contrasting forms in each sex (such as copulatory behaviours); sex differences in which an end point is found on a continuum on which the male and female average differs; and sex convergence and/or divergence, in which the end point is the same in both sexes but the underlying neural mechanisms are different[52]. The distinction between the latter two types can be considered the difference between 'quantitative' and 'qualitative' sex differences. Although attention has mostly been paid to documenting quantitative sex differences in pain, a growing number of examples of qualitative differences in pain have been reported[31,39,43,53–64], and these promise to be far more important in the long run. As a practical matter, analgesics are routinely titrated according to their effect, which will effectively mitigate any sex differences along with other sources of inter-individual variability. Convergence or divergence in mechanisms underlying pain modulation in the sexes, by contrast, has direct and important consequences for analgesic drug development.

Explanations of sex differences can be grouped into various categories (BOX 3). For example, one can ask about the reason that sex differences exist (the ultimate cause) or the mechanisms underlying them (the proximate cause). Two hypotheses have been put forward regarding the ultimate causes of sex differences in pain and analgesia. One suggests that male and female mammals are under divergent adaptive pressure with respect to the evolution of pain modulatory circuitry owing to the presumably more common exposure to traumatic pain in males and visceral pain in females. However, there seems to be no extant data directly supporting this possibility. A second idea is based on the observation that the neural systems underlying lordosis behaviour and analgesia in rats have extensive anatomical and neurochemical overlap (for example, both feature important roles for opioid receptors in midbrain loci such as the periaqueductal grey). The theory postulates that pain inhibitory circuitry may thus have 'piggybacked' on top of previously existing reproductive circuitry in the midbrain and brain stem[65]. According to this view, the reason for sex differences in analgesia is simply that there are already sex differences in reproductive behaviour.

Of perennial interest is the extent to which sex differences are due to sex-specific physiologies that are determined developmentally or to shared physiologies that are reversibly modulated in adulthood by gonadal steroids, the levels of which vary dramatically between the sexes. Evidence for organizational versus activational effects of gonadal hormones on pain traits is mixed, with some studies showing robust effects of neonatal male castration and female testosterone-induced masculinization on pain behaviour[66–70] and others being strongly supportive of the primacy of circulating hormone levels in the adult[71–77]. The classic organizational versus activational dichotomy has recently been supplemented by the realization that direct genetic effects are possible as well: traits such as pain might be affected by genes on the Y chromosome, X-linked genes escaping inactivation, parentally imprinted genes and/or allelic mosaicism[78]. Using the 'four core genotypes' model[79], such genetic effects on acute thermal and tonic inflammatory pain have been observed[80,81], although the precise mechanism underlying the increased pain sensitivity of XX-containing (but not necessarily gonadally female) mice is not yet known.

A number of more specific explanations for sex differences in pain have been put forward, spanning the range of the sociological, psychological and biological sciences (BOX 3). Some of these explanations purport that sex differences in pain are essentially an artefact. For example, it has been asserted that the on pain scales, the pain label "worst pain imaginable" is probably affected by childbirth experience[82] such that the overall size of the pain scale is larger in most women than in men. If so, a woman's five out of ten numerical rating would actually represent higher pain perception than the same rating given by a man. Another example concerns gender role expectations, which are due to sex-specific socialization. Males may be discouraged from expressing pain behaviours, whereas females are 'permitted' to do so, which might lead to biased reporting in one sex and not the other[83]. Other explanations purport that sex differences in pain are secondary to known sex differences in some other experience (such as abuse), psychological state (such as anxiety) or strategy (such as coping) that is known to affect pain. For example, if depression is associated with worsened pain and women are more likely to experience depression, women will have more pain for a reason lying outside the core of pain physiology. In a number of studies, controlling for one of these variables completely abolished the observed sex differences[84–87].

Explanations rooted explicitly in pain biology, either at the systems level or neurochemical level, purport that aspects of neural processing of pain feature either quantitative or qualitative sex differences. Three such explanations — involving

Box 2 | **Are there sex differences in laboratory pain sensitivity?**

A recent review[15] summarized the results of 122 studies of sex differences in laboratory pain sensitivity that were published between 1998 and 2008. The authors noted that many studies did not observe statistically significant sex differences and "have not [produced] a clear and consistent pattern of sex differences in human pain sensitivity". This analysis would seem to suggest that the hypothesis of sex differences in experimental pain might be untrue and largely due to selection and reporting bias. However, determining the presence or absence of sex differences based on statistical tests conflates the research question itself with the statistical power and design of the experiments. If there truly are no differences in laboratory pain between men and women, then the absolute differences of male–female comparisons should be randomly distributed around zero. The figure shows the results of testing this hypothesis by noting the direction of the sex difference reported by each paper included in the review (except for two papers, which were unavailable). For 14.7% of individual findings, the direction of the nonsignificant sex difference was not reported (only the *p* value was); these cases are excluded. In the figure, dark pink bars represent studies in which females were significantly more pain sensitive (that is, they had lower thresholds or tolerances, and higher ratings) than males by the dependent measure shown (across modalities; top four graphs) or on the modality shown (across measures). Dark purple bars represent studies in which males were significantly more pain sensitive than females. Also shown, however, are studies in which all reported (nonsignificant) differences were in the same direction (medium pink and purple tones), and studies in which the plurality of reported differences were in that direction (light tones). Green bars (F=M) show studies in which an equal number of reported measures showed sex differences in each direction, or in which a single reported measure showed a precisely equal mean value in each sex. Statistical significance levels were obtained by comparing the obtained 'pink' and 'purple' totals to a balanced distribution using the χ^2 test. The figure demonstrates that there can be absolutely no doubt about the existence of sex differences in pain sensitivity, although their size and importance are still debatable.

qualitative sex differences in the midbrain, spinal cord and the primary afferent — are currently more comprehensively documented than the others.

Multiple laboratories have observed that the midbrain–brain stem neural circuit subserving stress-induced analgesia, κ-opioid (and possibly μ-opioid) analgesia, morphine tolerance and morphine hyperalgesia in mice contains NMDA-type glutamate receptors (NMDARs) in males[49,56,57,88–90] but not females; in many cases, females seem to use melanocortin 1 receptors (MC1Rs) instead[39,54,91]. In these studies, pharmacological antagonism with non-competitive NMDAR antagonists (for example, MK-801) blocks the phenomena in male but not female mice at any dose. In female subjects, genetic dysfunction or pharmacological antagonism of MC1R does not actually block the phenomena but instead renders them newly sensitive to blockade by MK-801. Similarly, ovariectomy leads to MK-801 sensitivity, whereas chronic oestrogen or acute progesterone treatment reinstates resistance to MK-801. The parsimonious interpretation of this body of research would suggest that two alternative pathways exist for opioid analgesia and hyperalgesia; one (the NMDAR pathway) normally used by males and one (the MC1R pathway) normally used by females. Depending on hormonal levels, females can access the 'male' system when their own system is compromised. Although most of the research has been carried out in mice, for κ-opioid analgesia this sex difference is seen in humans as well, with genetic dysfunction of *MC1R* leading to increased pentazocine analgesia in women but not men[39].

Studies have documented that the neural circuitry subserving analgesia from sex steroids and morphine in the rat spinal cord show profound sex divergence[60,61,92], and recent work suggests that the core of the sex difference stems from a bias in μ- and/or κ-opioid heterodimer expression[59,93]. These heterodimers — the formation of which is under regulation by spinal oestrogen synthesis[93] — are vastly more prevalent in the female rat spinal cord than in the male spinal cord and are activated by endogenous dynorphin 1–17, which itself can be released by intrathecal injection of morphine, producing effects that are not seen in monomeric κ-opioid

Box 3 | **Categories of explanation for sex difference in pain and analgesia**

The proposed explanations for sex differences in pain and analgesia can be split into two groups: the ultimate causes, which aim to explain why there is a sex difference, and the proximate causes, which aim to explain how the sex difference is instantiated. The divergent evolutionary pressure hypothesis and the reproduction–pain co-evolution hypothesis[65] are both examples of possible ultimate causes. Proximate causes can be split into various categories, which are outlined below along with examples and example references.

Experiential
Sex difference is due to differential painful experiences (absolute or relative) by sex or experiences that can affect pain, such as abuse[108], clinical pain frequency[109], familial pain history (pain modelling)[110] and labour pain affecting scale usage[82].

Psychological
Sex difference in pain is due to sex differences in psychological states or strategies that themselves modulate pain experience, including: anger and negative affect[112]; anxiety, anxiety sensitivity and fear[113]; catastrophizing, fear-avoidance and somatic awareness[86]; coping[114]; and self-efficacy and perceived control[87].

Genetic
Sex difference is due to sex chromosome effects, leading to sex-specific pain physiology[81]. Such sex-specific effects could arise from buffering from allelic mosaicism, X chromosome gene imprinting, X chromosome genes escaping inactivation or genes on the Y chromosome.

Neurochemical
Sex difference in pain is due to sex-dependent levels or functioning of pain-related neurochemicals and/or their receptors; for example: adenosine receptors[122]; cannabimimetic lipids[123]; cyclic AMP response element-binding protein[124]; cytokine expression[125]; G protein-gated inwardly rectifying K^+ channels[62]; monoamine receptors[126]; neuregulin 1 (REF. 127); neurosteroids[128]; NMDA receptors[129]; NMDA versus melanocortin 1 receptors[54]; opioids and opioid receptors[130]; opioid receptor dimerization[59]; opioid and monamine receptor synergy[61]; orphanin FQ/nociceptin[131]; peptide content and release[132]; protein kinases[96]; and Toll-like receptor 4 (REF. 53).

Organizational
Sex difference is due to steroid action on development, leading to sex-specific pain physiology[67].

Activational
Sex difference is due to steroid action in adulthood, modifying common pain physiology. Steroids with sex-specific pain-associated effects include androgens[53], oestrogens[107] and progesterone[81].

Systems level
Sex difference in pain is due to sex differences in systems level biological phenomena mediating or affecting pain, such as cardiovascular system modulation[115], collateral sprouting of noninjured axons[116], cortical connectivity[117], diffuse noxious inhibitory controls[118], inflammation[119], midbrain–brainstem connectivity[120] and vagal nerve modulation[121].

Sociocultural
Sex difference is due to sociocultural differences between men and women, including differences in gender roles[111] and gender role expectations[84].

receptors[59]. These results may explain the known dependency of morphine analgesia in female (but not male) mice on the κ-opioid receptor gene[41].

Robust regulation of pain-relevant signal transduction pathways, especially those involving protein kinases Cε, Cδ and A, by sex hormones has been observed[63,94–96]. Investigators have shown, for example, that hyperalgesia induced by the activation of β_2-adrenergic receptors is dependent on protein kinase Cε in male but not female rats[94]; this effect is mediated by direct oestrogen inhibition of the peripheral nociceptor[95].

Perhaps the biggest conceptual difficulty in explaining sex differences in pain and analgesia is that many of the proposed explanations seem fully able to account for observed differences. Can they all be simultaneously true? Of course, it is entirely conceivable that these explanations interact with each other. For example, if the feminine gender role dictates that pain will be more intense, that would be associated with expectancies for increased pain, which could engage pain facilitatory systems (much like a nocebo effect) and neurochemical elements associated with them (such as cholecystokinin and cannabinoid 1 receptors[97,98]) in a sex-dependent manner.

Future directions

The subfield of sex differences in pain is at an interesting juncture: some still doubt that there is anything to be studied or anything worth studying, whereas others are well into their search for underlying mechanisms. As mentioned above, most preclinical researchers simply ignore the issue entirely. Why are female rats and mice avoided? I believe that the simple combination of inertia and fear of oestrous cycle-related variability are sufficient explanations and that this fear is, in fact, unfounded. The sex-specific coefficients of variation (mean-corrected standard deviations) have been examined in large archival data sets using acute thermal and tonic inflammatory pain tests in mice[7], and in fact it is male mice that generally display (nonsignificantly) higher variability. Whatever oestrous cycle-related variability there might be, dominance hierarchies (and associated fighting) in cages of male mice provide a male-specific source of variability that may be equal or greater in magnitude.

Although I contend that the evidence for both clinical and experimental sex differences is overwhelming, it is true that the clinical impact of this research is very limited at this point in time[20]. I believe this is because most investigators continue to study quantitative sex differences in pain instead of focusing on the far more important qualitative differences. Regardless of the overall sensitivity of men and women to pain and pain inhibition, ignoring sex-specificity in neural circuits subserving these phenomenon will continue to complicate drug development efforts. There are already too many examples of qualitative sex differences in pain biology to simply assume that similar biological mechanisms exist in male and female subjects. Wilful blindness to sex differences risks both overgeneralizing findings made in male subjects and missing the opportunity to discover female-specific mechanisms. The Toll-like receptor 4 (TLR4) sex difference described in BOX 1 is a perfect example. Those findings predict that spinal TLR4 antagonism, even if it is successful in blocking pain in men, would be ineffective in women. However, findings from my group's research necessitate the existence of an as-yet-uncharacterized alternative (non-TLR4) mechanism. Given that women with chronic pain greatly outnumber men, to ignore female-specific pain biology is to do a great ethical disservice to the majority of people with this condition.

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