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A systematic literature review of 10 years of research on sex/gender and pain perception – Part 2: Do biopsychosocial factors alter pain sensitivity differently in women and men?

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ABSTRACT

This systematic review summarizes the results of 10 years of laboratory research on pain and sex/gender. An electronic search strategy was designed by a medical librarian to access multiple databases. A total of 172 articles published between 1998 and 2008 were retrieved, analyzed, and synthesized. The second set of results presented in this review (129 articles) examined various biopsychosocial factors that may contribute to differences in pain sensitivity between healthy women and men. The results revealed that the involvement of hormonal and physiological factors is either inconsistent or absent. Some studies suggest that temporal summation, allodynia, and secondary hyperalgesia may be more pronounced in women than in men. The evidence to support less efficient endogenous pain inhibitory systems in women is mixed and does not necessarily apply to all pain modalities. With regard to psychological factors, depression may not mediate sex differences in pain perception, while the role of anxiety is ambiguous. Cognitive and social factors appear to partly explain some sex-related differences. Finally, past individual history may be influential in female pain responses. However, these conclusions must be treated with much circumspection for various methodological reasons. Furthermore, some factors/mechanisms remain understudied in the field. There is also a need to assess and improve the ecological validity of findings from laboratory studies on healthy subjects, and perhaps a change of paradigm needs to be considered at this point in time to better understand the factors that influence the experience of women and men who suffer from acute or chronic pain.

1. Introduction

Hundreds of laboratory studies on the role of sex in human pain perception have been published between 1998 and 2008, but it is difficult to draw a clear pattern of responses that distinguishes women from men. As shown in our companion review published in this issue of *Pain*® [157], differences in pain sensitivity observed in healthy females (F) and males (M) are not always consistent across different experimental pain modalities or are absent. Clinically, however, it is well documented that women are more likely than men to report a variety of recurrent pains, in multiple body areas, which are often described as being more severe and frequent compared to men [17,60,132,194]. Therefore, numerous laboratory studies have been conducted to try to understand the mechanisms underlying these differences (see reviews by Fillingim [52], Fillingim et al. [60], Mogil [132], Myers et al. [134], Robinson et al. [164], Rollman et al. [168]).

Until a few years ago, a large majority of studies used the terms "sex" and "gender" interchangeably. However, an important distinction has been made between the 2 terms: "sex" refers to biological differences between women and men according to their

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reproductive organs, whereas "gender" refers to a broader and more complex psychological, environmental, sociocultural, and political framework that encompasses the characteristics ascribed to each sex that are generally accepted and influenced by society (gender role) [19,51,88,134,141,202]. The Sex, Gender and Pain Special Interest Group of the International Association for the Study of Pain produced a consensus report to provide practice guidelines for future research [79]. It pointed out that gender should be viewed as a continuum on which an individual is somewhere in the range from exclusively masculine to exclusively feminine, while sex refers to the dichotomous concept of being M or F [79]. The authors of these guidelines also suggested that when feasible, both constructs should be examined to derive a better understanding of their relative contribution to the differences in pain reported by F and M.

Over the years, laboratory research has focused on the biological factors that could potentially mediate sex-related differences in pain responses. The role of psychological and social determinants has also been amply investigated. What have we learned in 10 years of laboratory research into the role of these factors on sex differences in pain perception? What is the clinical significance of the findings obtained? To our knowledge, only 1 recent review of the literature [150] used a systematic method [34,49] to examine studies on the factors that could account for differences in pain perception between F and M. (Riley et al. [162] conducted a meta-analysis of studies on pain perception across the menstrual cycle but did not examine those that included M for comparison.) However, the review by Popescu et al. [150] is limited to only one biological aspect: pain modulation by diffuse noxious inhibitory controls (DNICs).

The purpose of the present article is to provide a comprehensive, rigorous, and critical summary of the laboratory research between 1998 and 2008 that examined the role of various biological, psychological, and social factors that may contribute to sex differences in pain sensitivity in healthy women and men via a systematic approach to review the literature.

2. Methods

This systematic review was conducted according to guidelines from the Centre for Reviews and Dissemination [29] and the PRISMA Statement [33]. All procedures employed to retrieve, screen and determine study eligibility are reported in Figure 1 of the companion paper [157]. A total of 172 articles published between 1998 and 2008 met the eligibility criteria, but only those that examined the extent to which various biopsychosocial factors may influence sex-related pain perception (ie, pain threshold [PTh], pain tolerance [PTol], pain intensity [PInt], and/or pain unpleasantness [PUnp]) were included in the present paper. Studies that measured biopsychosocial factors but did not assess the significance of interrelations with sex and pain sensitivity were excluded from the review. A total of 129 out of 172 articles that met the above selection criteria were analyzed and synthesized. As mentioned in our companion paper [157], it was not possible to use a meta-analytic approach given (1) the nature of the primary objective of our work, (2) the broad scope of the topic, (3) the significant heterogeneity of the study methods, (4) the frequent lack of sufficient or adequate information to calculate effect sizes, and (5) the magnitude of the task of combining a systematic review of 129 articles to a meta-analytic methodology. As a result, the present review, although systematic and comprehensive, remains a narrative one with all the limitations it encompasses, including the absence of exact information about the potential influence of methodological variability on the detection of presence/absence of sex differences.

3. Results

3.1. Biological factors

Various biological mechanisms have been proposed to explain sex-related differences in pain sensitivity, including hormonal factors and physiological factors. Other possible explanations include sex differences in the central processing of nociceptive information and endogenous pain regulatory mechanisms.

3.1.1. Hormonal factors

3.1.1.1. Gonadal steroid hormones. The most obvious biological factor that primarily distinguishes M and F by its organizational and activational effects and could explain sex differences in pain sensitivity is exposure to gonadal steroid hormones. Compared to M, F have major fluctuations in estrogen and progesterone levels during the different phases of their menstrual cycle (MC). In contrast, androgens are essential for the development and maintenance of the M reproductive system; they are also present in F, but in a much lower quantity [6,191]. Between 1998 and 2008, there has been a growing amount of literature on the effects of gonadal hormones in human experimental pain sensitivity. No less than 7 review papers on this specific topic have been published since 1999 [6,7,38,39,63,162,176].

3.1.1.1.1. Menstrual cycle (MC). The following subsection focuses exclusively on human laboratory studies that measured variations in pain perception across the MC in F *and* included a group of M subjects. Twelve studies [1,3,4,36,82,97,98,109,110,124,169,189] chose to first compare the effect of MC phase on pain responses in F before examining sex-related differences in pain perception. None of them detected a significant effect of MC. (The study by Isselee et al. [89] was not included in the present review because the data reported in the Results section do not match those reported in the Discussion section.)

Four studies directly compared pain sensitivity in M vs F at different times of their MC. Drobek et al. [46] did not observe significant sex difference in pressure pain threshold (PP Th), in any of the MC phases, and this was true irrespective of the testing site. However, these results are questionable considering that menstrual phases were determined only by subject self-reporting. Gazerani et al. [67] examined the effect of MC on sex-related pain responses in a capsaicin model with a daily urine test to confirm ovulation time. Their results showed that, in comparison to M, F reported significantly higher peak PInt and a larger area of brush-evoked allodynia during their menstrual phase (when estrogen is at its lowest level) but not during their luteal phase (when both estrogen and progesterone levels are high). However, this pattern of results was not observed on the other outcome measures (PInt measured by the area under the curve PInt, pain distribution). Kowalczyk et al. [112] measured responses to cold pain (CP) in M and F 5 times during the MC on 2 separate occasions (2 sessions $\times$ 5 phases). Plasma estradiol and progesterone levels were assessed on each occasion, and ovulation was confirmed by a luteinizing hormone surge test. The results showed no significant sex difference for PTh or PTol, irrespective of the MC phase. However, the authors acknowledged the lack of statistical power of their study, thereby questioning the validity of their own results. Finally, Smith et al. [177] conducted an elegant study in which they compared pain sensitivity in M vs F in low- and high-estrogen states. The former state corresponded to the follicular phase of the MC. Transdermal micronized estradiol (0.4 mg) was administered daily to F to induce a high-estrogen state. Positron emission tomography served to examine activation of the μ-opioid neurotransmitter system during sustained deep pain induced by a 5% hypertonic saline injection in the masseter muscle. When F in the low-estrogen

condition were compared to M, they showed significantly less regional activation of the endogenous opioid system. When these same F were in the high-estrogen state, the pain stimulus induced regional activation of this neurotransmitter system, which was comparable to that observed in M. However, the changes in endogenous opioid tone did not translate into significant differences in the PInt ratings of M and F whether they were in the low- or high-estrogen state.

3.1.1.1.2. Exogenously administered estrogens. To further understand the role of gonadal hormones in sex-related differences in pain sensitivity, some researchers investigated the effects of oral contraception (OC) by comparing healthy F who were users (F/OC+) or nonusers (F/OC−) to their M counterparts. (It should be noted that none of the studies listed in this section took into account the type and nature of OC in their analysis.) Eight studies [1,3,26,36,151,169,188,189] chose to first compare the pain responses of F/OC+ and F/OC− before examining sex-related differences in pain perception. All of them showed that the responses of F/OC users and nonusers did not differ significantly, irrespective of the type of pain stimulus tested (heat, cold, glutamate, and muscle pain induced by exercise). Four studies directly compared pain perception in M vs F/OC+ and F/OC−. Bragdon et al. [21] reported inconsistent results, depending on the painful stimulus type. When exposed to heat pain (HP), M subjects exhibited higher PTh and PTol than F/OC−, but not if compared to F/OC+. With regard to ischemic pain (IP), F/OC+ presented a lower PTh than M and F/OC−, while the latter 2 groups were comparable. In a capsaicin pain model, Baad-Hansen et al. [12] observed that F/OC+ reported lower PInt than F/OC− in the early phase after capsaicin application (2–3 min), and lower pain scores than M in the later phase (5–11 min). The differences did not reach statistical significance for PUnp.

Drobek et al. [46] studied the PP Th in the masseter and temporalis muscles and found no differences between M vs F/OC+ and F/OC−. When the same stimulus was applied to the finger, F (OC+ and OC−) had a lower PTh than M, but only in their follicular phase. In a more recent study, Kowalczyk et al. [112] examined sex differences in response to a cold-pressor test (CPT) in F/OC−, F/OC+, and M. Testing occurred during 5 phases of the MC (menstrual, follicular, ovulatory, luteal, late luteal) and was repeated twice (10 sessions). The 3 groups did not differ significantly in terms of PTh or PTol.

The single study that examined the effects of hormonal replacement therapy [55] found that postmenopausal F on this type of treatment exhibited significantly lower HP Th and Tol than their M counterparts and F not on hormonal replacement therapy.

It is important to realize that the sex-related differences in pain sensitivity observed in some of the above studies are of a relatively small magnitude and are not necessarily significant across all pain modalities, tested sites, and/or outcome measures. Furthermore, it is difficult to draw clear conclusions from some of them due to methodological limitations with regard to limited simple size, experimental session timing across the MC, nomenclature employed to identify phases in the cycle, and lack of biological markers to track stage of the cycle (eg, urine testing, blood sample). In such a situation, it is not surprising that the effects of estrogens on pain responses are absent, minimal, or inconsistent. For a further discussion of the above methodological issues, the reader is referred to papers by Dao and LeResche [41], Greenspan et al. [79], and Sherman and LeResche [176].

3.1.1.2. Stress hormone (cortisol). Research has established that exposure to acute stress may attenuate pain perception [5,93]. We identified 4 studies published between 1998 and 2008 [3,4,45,207] that investigated whether cortisol, a central component of the stress response, was differentially affected by pain stimulation in F and M healthy subjects.

A study by al'Absi et al. [4] showed that M reported lower PInt than F during and after a CPT, but both groups presented a comparable elevation in salivary cortisol concentrations. However, a significant negative correlation was found between pain ratings and cortisol levels in M, but not in F. In a subsequent study, al'Absi and Petersen [3] preceded the CPT by a rest condition or a stress condition (see also Section 3.1.5.2) and confirmed their previous results [4], but only in the rest condition. Zimmer et al. [207] reported a significantly greater increase in cortisol levels during a CPT in M than F, but it did not translate into significant sex differences on the various pain measures used except one (PTol) in the second of a series of 2 trials. Using the same type of pain stimulus but a much larger sample size than previous studies, Dixon et al. [45] found that cortisol levels were significantly affected by duration of the stimulus (PTol) in both sexes, and M tolerated pain longer than F. Even when sex differences in PTol times were accounted for statistically, M demonstrated more cortisol reactivity than F. Further research is needed to elucidate the role of variations in adrenocortical activity on sex differences in pain perception.

3.1.2. Physiological factors

3.1.2.1. Blood pressure (BP) regulation. Considerable attention has been paid to blood pressure (BP) between 1998 and 2008, both as a predictor of the pain response (resting BP) and as a consequence of pain experience (BP reactivity) in M and F. Some evidence shows that sex differences in pain sensitivity could be related to the fact that M usually have higher BP, and that this elevation in BP could activate pain-modulating mechanisms, such as baroreceptor neural pathways and endogenous opioid systems that, in turn, could reduce pain responses [25,47,74,158,205]. We identified a total of 25 studies that examined the relationship between pain sensitivity and resting BP or BP reactivity in M and F.

Table 1 shows that most of the studies did not find a differential association between *resting* BP and pain responses in F and M. If we exclude studies that examined sex differences in BP *reactivity* during painful stimulation and obtained inconsistent results for systolic and diastolic BP, about half of the rest found a greater increase in BP reactivity in M than in F, while the other half showed comparable BP changes in both sexes. The type of nociceptive stimulus deployed to induce BP changes may explain the discrepancy in the findings, since it is known that different pain stimuli evoke distinct patterns of autonomic reactivity [185].

3.1.2.2. Heart rate (HR) and electrodermal reactivity. A large number of studies investigated whether heart rate (HR) reactivity to an experimental painful task differs between F and M. Table 2 shows that the majority of them (15/21) found either no HR change or comparable variations in both sexes. The other studies noted significant sex differences but in the opposite direction (greater HR increase in M or F). Although a much smaller number of studies examined electrodermal reactivity to experimental pain, all of them except one found no distinctive pattern within sex.

Taken together, the above studies failed to support the view that sex-related differences in pain perception could be accounted for, at least in part, by greater BP, HR, and skin conductance level (SCL) in M than in F.

3.1.3. Peripheral sensitization of the nervous system

Peripheral sensitization, also known as primary hyperalgesia, is an exaggerated response to a painful stimulus that occurs as a consequence of nociceptor sensitization at the periphery. To assess if some sex differences in pain perception could be partly attributed to such a mechanism of action, a total of 8 studies published between 1998 and 2008 compared PP Th after induction of deep pain. Five of them observed a comparable reduction of PP Th in both sexes at the injection site of glutamate [69,71,188] or at the muscle site following induction of delayed onset soreness [40,139]. Ge

Table 1
Studies on sex differences in pain perception and blood pressure.

Authors	Year	Sample size			Pain stimulus	Results
		Tot	F	M		
Resting blood pressure[a]						
France and Suchowiecki [64]	1999	83	44	39	NFR	- No association between PTh and SBP in both sexes - No association between PTh and DBP in both sexes
Helfer and McCubbin [81]	2001	55	29	26	CP	- Significant association between PInt and SBP in both sexes - Significant association between PInt and DBP in both sexes - Significant association between PInt and MAP in both sexes
Koltyn et al. [111]	2001	31	16	15	PP	- No association between PTh and SBP in both sexes (2/2 conditions) - Significant association PTh and DBP in M only (1/2 conditions)
Myers et al. [135]	2001	104	50	54	CP	- No association between PTh or PTol and SBP in both sexes
Bragdon et al. [21]	2002	42	20	22	HP	- Significant association between PTh and SBP in M only (2/2 conditions). Same results for PTol (1/2 conditions) - No association between PTh or PTol data on DBP (2/2 sessions) in both sexes
					IP	- No association between PTh or Tol and SPB in both sexes - No association between PTh or Tol and DPB in both sexes
Poudevigne et al. [151]	2002	42	21	21	MP	- No association between PInt and SBP in both sexes - No association between PInt and DBP in both sexes
Campbell et al. [27]	2004	135	59	76	IP	- No association between PInt or PUnp and SBP in both sexes - No association between PInt or PUnp and DBP in both sexes
al'Absi et al. [2]	2005	137	59	78	NRF	- No association between PInt and SBP in both sexes.
Blood pressure reactivity[a]						
Nyklicek et al. [141]	1999	20	9	11	EP	- Greater ↑ of SBP in M than F - Greater ↑ of DPB in M than F
Pinerua-Shuhaibar [147]	1999	43	25	18	IP	- No sex difference in MAP
Hellström and Lundberg [82]	2000	41	22	19	CP	- Greater ↑ of SBP in M than F - No sex difference in DBP
Helfer and McCubbin [81]	2001	55	29	26	CP	- Greater ↑ of SBP in M than F - Greater ↑ of DPB in M than F - Greater ↑ of MAP in M than F
Koltyn et al. [111]	2001	31	16	15	PP	- Greater ↑ of SBP in M than F (1/2 trials) - Greater ↑ of DBP in M than F (2/2 trials)
Myers et al. [135]	2001	104	50	54	CP	- No sex difference in SBP and DPB
Rollnik et al. [169]	2001	80	40	40	IP	- ↑ of SBP in F but not in M. - No sex difference in DBP
al'Absi et al. [4]	2002	65	34	31	CP	- No sex difference in SBP - No sex difference in DBP
Fillingim et al. [54]	2002	68	35	33	IP	- Greater ↑ of SBP in M than F - Greater ↑ of DPB in M than F
Poudevigne et al. [151]	2002	42	21	21	MP	- Greater ↑ of SBP in M than F - Greater ↑ of DPB in M than F
Lowery et al. [123]	2003	81	39	42	CP	- No sex difference in SBP - No sex difference in DBP
Dixon et al. [45]	2004	203	112	91	CP	- Greater ↑ of SBP in M than F but - Comparable ↑ in DPB in both sexes
al'Absi et al. [2]	2005	137	59	78	NFR	- Greater ↑ of SBP in M than F - No sex difference in DBP
Fillingim and Edwards [56]	2005	110	56	54	IP	- No sex difference in SBP - No sex difference in DBP
George et al. [73]	2006	66	34	32	CP	- No sex difference in SBP
Quiton and Greenspan [155]	2007	62	30	32	EP	- No sex difference in SBP - No sex difference in DBP
Hoeger Bement et al. [86] (Experiment 3)	2008	22	11	11	MP	- Greater ↑ of MAP in M than F

Tot, total; F, female; M, male; NFR, nociceptive flexion reflex; PTh, pain threshold; SBP, systolic blood pressure; DBP, diastolic blood pressure; CP, cold pain; PInt, pain intensity; PP, pressure pain; PTol, pain tolerance; HP, heat pain; IP, ischemic pain; MP, muscle pain; PUnp, pain unpleasantness; MAP, mean arterial pressure; EP, electrical pain.
[a] Results of al'Absi et al.'s study [1] were not included because these authors found significant interaction effects of sex and parental history for hypertension on pain ratings.

et al. [70,72] administered hypertonic saline but did not report any peripheral sensitization to PP at the injection site in both F and M. Similar observations were made by Plesh et al. [148] using a model of jaw exercise-induced pain. In summary, the above results suggest that there would not be sex-related differences in peripheral sensitization to PP following the induction of deep pain.

3.1.4. Nociceptive input processing and integration in the central nervous system (CNS)

Differences in cortical processing of noxious information could account for some of the sex-related variation in pain sensitivity. However, the relative role of this factor remains largely unexplored. In contrast, the possibility of differential nociceptive input integration in the central nervous system (CNS), leading to facilitation of excitatory synaptic responses (eg, wind-up, secondary hyperalgesia), has been studied more extensively between 1998 and 2008.

3.1.4.1. Central processing of nociception. Chapman et al. [31] tested phasic pupil dilation as a physiological marker of preconscious brain activity and found no sex-related differences in healthy volunteers submitted to electrical pain (EP) stimuli of varying intensity. However, brain-evoked potentials were also measured, and M demonstrated significantly greater evoked potential peak amplitude and peak latency than F at 150 ms after the end of stimulation. Nevertheless, this result remains difficult to interpret from a

Table 2
Studies on sex differences in pain perception and heart rate or electrodermal reactivity.

Authors	Year	Sample size			Pain stimulus	Results
		Tot	F	M		
Heart rate						
al'Absi et al. [1]	1999	128	46	82	CP	- Greater ↑ of HR in M than F
France and Suchowiecki [64]	1999	83	44	39	NFR + IP	- Comparable ↓ of HR in both sexes (DNIC)
Nyklicek et al. [141]	1999	20	9	11	EP	- No sex difference in HR
Zeichner et al. [206]	2000	42	24	18	CP	- Greater ↑ of HR in F than M
Helfer and McCubbin [81]	2001	55	29	26	CP	- No sex difference in HR
Koltyn et al. [111]	2001	31	16	15	PP	- No sex difference in HR (2/2 trials)
Myers et al. [135]	2001	104	50	54	CP	- Greater ↑ of HR in M than F
Rollnik et al. [169]	2001	80	40	40	IP	- No sex difference in HR
al'Absi et al. [4]	2002	65	34	31	CP	- No sex difference in HR
Fillingim et al. [54]	2002	68	35	33	IP	- No sex difference in HR
Lowery et al. [123]	2003	81	39	42	CP	- No sex difference in HR
Dixon et al. [45]	2004	203	112	91	CP	- Comparable ↑ of HR in both sexes
Frot et al. [65]	2004	20	10	10	ChP	- Comparable ↑ of HR in both sexes
Fillingim and Edwards [56]	2005	110	56	54	IP	- No sex difference in HR
al'Absi et al. [2]	2005	137	59	78	NFR	- Greater ↑ of HR in F than M
Tousignant-Laflamme et al. [193]	2005	39	20	19	HP	- Comparable ↑ of HR in both sexes
Garofalo et al. [66]	2006	66	44	22	CP	- No sex difference in HR
					HP	- No sex difference in HR
Aslaksen et al. [10]	2007	64	32	32	HP	- Greater ↑ of HR in M than F
Quiton and Greenspan [155]	2007	62	30	32	EP	- No sex difference in HR
Hoeger Bement et al. [86] (Experiment 3)	2008	22	11	11	MP	- Comparable ↑ of HR in both sexes
Electrodermal reactivity						
Tousignant-Laflamme et al. [193]	2005	39	20	19	HP	- Comparable ↑ of SCL in both sexes
Garofalo et al. [66]	2006	66	44	22	HP	- No sex difference in SCL
Aslaksen et al. [10]	2007	64	32	32	HP	- Greater ↑ of SCL in M than F
Quiton and Greenspan [155]	2007	62	30	32	HP	- Comparable ↑ of SCL in both sexes

Tot, total; F, female; M, male; CP, cold pain; HR, heart rate; NFR, nociceptive flexion reflex; IP, ischemic pain; DNIC, diffuse noxious inhibitory controls; EP, electrical pain; PP, pressure pain; MP, muscle pain; ChP, chemical pain; HP, heat pain; MP, muscle pain; SCL, skin conductance level.

clinical perspective and in view of the fact that no sex difference was noted in PInt.

Three other studies investigated cortical-evoked potentials in healthy subjects submitted to an experimental pain task. Lundström et al. [125] administered noxious intranasal trigeminal stimuli and recorded event-related potentials at 6 positions (CZ, PZ, C3, C4, P3, and P4). They reported that F compared to M had significantly larger amplitudes for only the P3 component in both hemispheres in response to noxious stimulation. Their results also showed that F had overall higher amplitudes and shorter latencies than M. The only hemispheric difference between F and M was shorter latencies for F in the left hemisphere. However, it is important to point out that all these effects were not correlated to the subjects' pain ratings, which also did not differ significantly between F and M. Another study showed comparable P1 latency and magnetoencephalographic amplitude in both sexes after painful oesophageal stimulation [85]. Chao et al. [30] F had significantly shorter N1 and P1 latencies after the application of HP stimuli on both the upper and lower limbs. P1 and N1–P1 amplitudes for the lower limbs (but not the upper limbs) and PInt were also significantly higher in F. These authors concluded to a faster activation of thermal nociception in F that may be of peripheral or central origin.

In a study of brain function asymmetries, Lugo et al. [124] characterized hemispheric lateralization for HP perception in a large sample of M and F subjects. Their results showed comparable sensory lateralisation in both sexes even though F reported significantly higher PInt scores than M, regardless of the hand.

Four studies compared patterns of brain activation in response to experimentally induced painful sensations in M and F. (Two often-quoted neuroimaging studies that examined sex differences in response to rectal distension were not included in the present review because it was not clear in the study by Berman et al. [18] if the induced sensation was painful, while in the study by Kern et al. [108], it was stated that the subjects did not experience pain.) The first 2 [44,144] undertook positron emission tomography and both of them demonstrated a considerable degree of overlap between sexes in spatial and PInt patterns of central activation during HP stimulation. However, Paulson et al. [144] observed greater activation in the contralateral thalamus and anterior insula in F subjects during HP who also rated the stimulus as being more painful than in M. This study also showed prefrontal activation in the right hemisphere in M and in the left hemisphere in F. The authors concluded that it was not possible to determine whether these differences in brain activation could be due to sex, perceived PInt, or both. To further elucidate this issue, Derbyshire et al. [44] equalized perceived HP Int across all subjects and noted a pattern of activation in the prefrontal cortex which was similar to that recorded by Paulson et al. [144], but they failed to replicate findings in the thalamus, thereby supporting the hypothesis of an association between greater HP sensitivity and thalamic activation in F compared to M. Contrary to Paulson et al. [144], Derbyshire et al. [44] provided evidence of greater activation of the parietal, SI, SII, and insula cortices in M than in F. In a more recent functional magnetic resonance imaging (fMRI) study, Moulton et al. [133] reported results in the direction opposite to those in the 2 above studies. Deploying HP stimuli that evoked the same PInt in both sexes, these authors demonstrated regional deactivation (rather than activation) in F compared to M, as evidenced by more negative blood oxygenation level-dependent signal responses in the primary sensory and prefrontal cortices. Another fMRI study was carried out by Henderson et al. [83], but it is difficult to draw any conclusions because the authors compared only the fMRI scans of M and F subjects who rated their pain as $\geqslant 3/10$, thereby introducing, in our opinion, a significant bias in their results, given that no sex difference emerged in the PInt ratings when all subjects were included in the analyses.

In summary, there are clearly not enough brain imaging data at this point to draw firm conclusions that go beyond speculation, and more extensive research with fMRI is needed.

3.1.4.2. Temporal summation (TS) of pain. Temporal summation (TS) is frequently considered in human research as an indicator of central facilitation of noxious stimuli. This phenomenon refers to the progressive augmentation of perceived pain while the intensity of repetitive or constant noxious stimuli remains constant [77,153]. Animal research (eg, [119,152]) has shown that such stimulation induces a progressive increase in the excitability of spinal cord neurons caused by wind-up of nociceptive activity.

Human experiments examining sex-related differences in TS of pain gave rise to 16 studies published between 1998 and 2008. Five of them found no sex difference in TS of HP or PP [115,116,138,181,192]. (The study by Chesterton et al. [32], which examined the effect of repeated application of PP stimuli, was excluded from the present review because the authors implemented a much longer interstimulus interval [14 trials over 1 h] than those used commonly [1–6 s].) Ayesh et al. [11] reached a similar conclusion with EP, although they observed significant differences in some of their outcomes but viewed them as being less meaningful. Seven studies revealed that F exhibited significantly greater TS after repetitive painful stimuli in various modalities, including HP and PP [43,56,59,62,80,167,173–175]. This was true not only in terms of reported subjective pain responses (eg, PInt, PUnp) but also for the TS Th (F < M) of the RIII reflex, which is viewed as an objective outcome [175]. Hastie et al. [80] submitted 188 healthy subjects to a series of pain tasks and conducted cluster analysis. Their results revealed 4 distinct clusters, one of which was associated with increased TS. The percentage of F (69%) was significantly higher in this cluster compared to M (31%).

Interestingly, Robinson et al. [167] found that anxiety and gender stereotypes about willingness to report pain explained a significant proportion of variation in the magnitude of TS of pain, and when these 2 factors were controlled in the statistical analysis, sex was no longer a significant predictor of TS. Sarlani et al. [173] did not identify any significant relationship between TS of pain and psychological factors, such as anxiety and depression, in either M or F.

Very few studies have examined whether there is a sex difference in TS of chemically induced muscle pain (MP). Ge et al. [71] investigated the effect of 2 consecutive glutamate injections administered at an interval of 5 min. Their results suggest greater susceptibility to the development of TS in F compared to M. However, the same authors [72] failed to replicate this finding in a hypertonic saline-evoked MP model (2 consecutive injections 45 s apart). (Studies by Cairns et al. [28], Svensson et al. [195], and Ge et al. [72] did not examine sex differences in TS of chemically induced MP because the second injection was administered after pain induced by the first injection disappeared.)

In summary, some evidence indicates that the TS phenomenon of pain is more pronounced in F than in M. However, certain data suggest that this mechanism could be itself modulated by psychological factors influencing pain perception [58,167].

3.1.4.3. Spatial summation (SS) of pain. Spatial summation (SS) of pain refers to the ability of the nervous system to integrate nociceptive information from spatially separated neurons at the same time, the larger the area of stimulation, the more pain being felt (while the painful stimulus remains constant). Only 3 studies between 1998 and 2008 tested the hypothesis that F may require smaller areas of stimulation than M to evoke similar pain responses. Lautenbacher et al. [116] reported no significant difference between F and M in HP Th, irrespective of stimulation area size. Defrin et al. [42,43] conducted 2 studies in which they observed no effect of sex on the magnitude of SS, irrespective of the pain stimulus (HP or CP).

3.1.4.4. Allodynia and secondary hyperalgesia. Allodynia refers to pain produced by a non-noxious stimulus, whereas secondary hyperalgesia is an exaggerated pain response to a nociceptive stimulus. Both phenomena are believed to be the result of a central sensitization process [114], although it is sometimes difficult to disentangle central from peripheral sensitization or to determine if both are involved. We identified 5 studies that compared the development of allodynia and/or secondary hyperalgesia in M and F after cutaneous sensitization. Gazerani et al. [67] noted that F showed a significantly greater area of brush-evoked allodynia after capsaicin sensitization. F were also found to exhibit a significantly larger area of secondary pinprick hyperalgesia following glutamate [69] and capsaicin injection [68]. After adjusting for estimated sex differences in forearm surface area, Jensen and Petersen [94] failed to discern a sex difference in areas of secondary pinprick hyperalgesia following capsaicin sensitization, but F reported a larger area of brush-evoked allodynia. Pedersen et al. [146] experimentally induced PP, CP, and HP in the lower part of the oesophagus and showed that F drew significantly larger referred pain areas irrespective of the stimulus, which, according to the authors, reflected sex differences in central pain processing. In summary, some evidence suggests that F are perhaps more inclined to develop allodynia and/or secondary hyperalgesia after cutaneous sensitization than their M counterparts.

3.1.5. Endogenous pain regulatory mechanisms

It is well known that pain perception is modulated by endogenous pain inhibitory systems, and a good deal of research between 1998 and 2008 was devoted to the role played by them in observed sex-related variations in pain sensitivity.

3.1.5.1. Diffuse noxious inhibitory controls (DNICs). DNICs refer to the antinociceptive effects of one source of pain by the application of a noxious stimulus on any parts of the body distant from neuronal excitatory receptive fields. Now referred to as conditioned pain modulation [204], this phenomenon has been repeatedly observed in animals and humans [197]. DNICs are mediated by spino-bulbospinal loops and a final postsynaptic inhibitory mechanism exerting effects on spinal wide-dynamic range neurons [117,118,196].

The human experimental paradigms developed for studying DNICs typically involve measurement of pain reactivity to a painful "test" stimulus before, during, and after application of a noxious "conditioning" stimulus to an anatomically remote area of the body. As enumerated in Table 3, we identified a total of 17 studies, involving 20 experiments, which tested the hypothesis that DNICs could be less efficient in F than in M. Sixty percent of these experiments (12/20, ie, Baad-Hansen et al. [12], France and Suchowiecki [64], Ge et al. – 1st injection [70,72], Lautenbacher et al. [115], Peddireddy et al. [145], Pud et al. [154], Quiton and Greenspan [155], Rosen et al. – Exp #1 and #2 [170], Tousignant-Laflamme et al. [192] and Weissmann-Fogel et al. [199]) failed to confirm this hypothesis. All these experiments found comparable DNIC inhibition in F and M using various types of experimental pain paradigms. It should be pointed out that Weissmann-Fogel et al. [199] did report a sex difference in DNICs but it was no longer significant after statistically controlling for pain catastrophizing (see Section 3.2.3.1).

Arendt-Nielsen et al. – Exp 2 [9], Granot et al. [78], and Serrao et al. [175] observed that DNICs were less efficient in F subjects than in their male counterparts. The results obtained by Arendt-Nielsen et al. [9] merit further comment as they point to the important complexity of sex-related differences in DNIC analgesia. When these authors applied MP (hypertonic saline injection) as the conditioning stimulus and PP as the test stimulus, they noted DNIC analgesia in M but not in F. When the conditioning stimulus was CPT, they observed DNIC analgesia in both sexes but it was significantly more pronounced in M. Finally, when they administered

Table 3
Studies on the efficiency of diffuse noxious inhibitory controls (DNICs) in healthy F and M subjects.

Authors	Year	Sample size			Conditioning stimulus	Test stimulus	DNIC effects	Sex difference
		Tot	F	M				
France and Suchowiecki [64]	1999	83	44	39	- IP tourniquet Site: R forearm	- Nociceptive flexion reflex (NFR) Site: L leg	Comparable ↓ NFR responses in both sexes	No
Staud et al. [181]	2003	33	22	11	- HP immersion, 47 °C for 16 s Site: L hand	- TS of HP contact thermode 53 °C 8 stimuli of 0.7 s each Site: R hand	↓ TS of HP in M but not in F	Yes
Svensson et al. [188]	2003	35	17	18	- 2 Glutamate injections Site: Masseter muscle	- PPA Site: Contralateral masseter muscle	No DNIC in both sexes	N/A
Ge et al. [70]	2004	21	10	11	- 2 Bilateral hypertonic saline injections Site: Trapezius muscles	- PPA Site: Posterolatera1 neck muscles	Comparable ↑ in PP Th in both sexes after the 1st injection which persisted significantly longer in M than in F No further ↑ in PP Th in M after 2nd injection and no DNIC in F after 2nd injection	No/Yes
Serrao et al. [175]	2004	36	20	16	- CPT 2–4 °C for up to 5 min Site: R hand	- TS of NFR Site: L leg	Greater ↓ of TS of NFR in M than in F	Yes
Baad-Hansen et al. [12]	2005	54	34	20	- CPT 1–2 °C for 3 min Site: Nondominant arm	- Topical capsaicin Site: R or L buccal gingiva	Comparable ↓ of PInt in both sexes	No
Ge et al. [71]	2005	28	14	14	- 2 Glutamate injections Site: Trapezius muscles	- PPA Site: Posterolatera1 neck muscles	No DNIC in both sexes	N/A
Peddireddy et al. [145]	2005	30	15	15	- Hypertonic saline injection Site: Temporalis muscle	- Nociceptive blink response (NBR) Site: Forehead	Comparable ↓ NBR responses in both sexes	No
Pud et al. [154]	2005	40	17	23	- CPT 1 °C for 30 s Site: R finger	- Mechanical stimulation punctuate Site: L hand	Comparable ↓ in PInt in both sexes	No
Ge et al. [72]	2006	30	15	15	- 2 Bilateral hypertonic saline injections Site: Trapezius muscles	- PPA Site: Posterolatera1 neck muscles	Comparable ↑ in PP Th in both sexes after the 1st injection Further ↑ in PP Th in M after 2nd injection and no DNIC in F after 2nd injection	No/Yes
Quiton and Greenspan [155]	2007	62	30	32	- EP Site: L forearm	- HP contact thermode Site: R calf	Comparable ↓ in HP Int in both sexes	No
Arendt-Nielsen et al. [9]	2008	20	10	10	Exp #1 - Hypertonic saline injection Site: L tibialis	- PPA Site: R knee	↑ in PP Th in M but not F	Yes
					Exp #2 - CPT 1–2 °C for 6 min Site: L hand	- PPA Site: R knee	Greater ↑ in PP Th in M than F	Yes
					Exp #3 - Hypertonic saline + CPT 1–2 °C for 5 min	- PPA Site: R knee	Comparable ↑ in PP Th in both sexes	No
Granot et al. [78]	2008	31	10	21	- Water bath 12 °C to 46.5 °C for 60 s Site: Dominant hand	- HP contact thermode between 45 °C to 47 °C for 10, 20 and 30 s[a] Site: Non-dominant forearm	Greater ↓ in HP Int in M than F	Yes
Lautenbacher et al. [115]	2008	40	20	20	- HP water tub 46 °C Site: L–R hands	- PPA Site: L–R fingers	Comparable ↓ in HP for TS Int in both sexes	No
Rosen et al. [170]	2008	30	15	15	Exp #1 - EP Site: Maxillary incisors Fingertips	- CPT 2–4 °C for 5 min maximum Site: Contralateral hand - CPT 2–4 °C for 6 min maximum	Comparable ↓ in EP Th in both sexes (1/2 sites) (No DNIC effect at the other site)	No
					Exp #2 - PPA Site: Masseter muscle Finger	Site: Contralateral hand	Comparable ↑ in PP Th in both sexes (2/2 sites)	No
Tousignant-Laflamme et al. [192]	2008	83	41	42	- CPT 7 °C, 10 °C or 12 °C for 2 min Site: R arm	- HP contact thermode [b] Site: L forearm	Comparable ↓ tonic HP Int and TS in both sexes	No
Weissman-Fogel et al. [199]	2008	48	29	19	- MP, elbow flexor 40 MVC Site: Dominant biceps	- HP contact thermode 47 °C for 1 min Site: Non-dominant hand	Comparable ↓ in HP Int in both sexes after controlling statistically for tendency to catastrophize in face of pain	No

Tot, total; F, female; M, male; L, left; R, right; IP, ischemic pain; NFR, nociceptive flexion reflex; HP, heat pain; TS, temporal summation; PPA, pressure pain algometer; Th, threshold; CPT, cold-pressor test; PInt, pain intensity; N/A, not applicable; EP, electrical pain; MP, muscle pain; MVC, maximum voluntary contraction.

[a] The temperature of test stimulation was determined individually to reach a pain rating of 60 out of 100 on the numeric rating scale.

[b] The temperature of test stimulation was determined individually to reach a pain rating of 50 out of 100 on the visual analogue scale.

the 2 conditioning stimuli concurrently, DNIC analgesia was considerably reduced in M to the point that it was comparable to what was observed in F. These authors [9] suggested that the 2 concurrent stimuli may have counteracted each other, thereby producing less DNIC in M than either individual conditioning stimulus.

A few studies examined sex differences in DNICs following repetitive nociceptive stimulation – that is, TS. Serrao et al. [175] reported that activation of DNICs through hand immersion in cold water increased TS of the nociceptive flexion reflex in F and M, but the effect was significantly lower in F. Staud et al. [181] demonstrated that DNICs significantly inhibited thermal wind-up pain in M only. However, 2 recent studies [115,192] failed to find any significant effect of DNICs on TS.

Ge et al. [70,72] conducted 2 sets of studies to more closely examine the temporal development of DNICs in M and F. They observed that both groups showed a parallel increase of PP Th after a first injection of hypertonic saline solution. When a second injection was administered in the same session, the hypoalgesic effect did not increase in M but lasted significantly longer than in F. In fact, there was no DNIC inhibition in F after the second injection. The results of these 2 studies contrast with those of Ge et al. [71], who did not succeed in inducing DNICs in either F or M with glutamate injections as the conditioning stimulus. The same was true in experiments by Svensson et al. [188]. In summary, a good number of studies published between 1998 and 2008 argue against sex differences in DNIC analgesia. Others support the hypothesis of a deficient (or absent) DNIC system in F and, when they do, the phenomenon appears complex and not necessarily applicable to all pain modalities.

3.1.5.2. Stress-induced analgesia (SIA). It is well known that acute stress events can reduce pain sensitivity via endogenous opioid and nonopioid systems [8,184,203]. Sternberg et al. [182] examined whether athletic competition is a stressor capable of initiating an analgesic response, and whether this response differs according to sex. Their results revealed that the direction of the response (analgesic or hyperalgesic) depended on the pain stimulus (CPT or HP), the body region tested, and the type of athlete (basketball players, fencers, track runners). Sex was not a significant factor in the observed variations. In a subsequent study, Sternberg et al. [183] further investigated different components of competition-induced analgesia (exercise-related stress vs cognitive aspects of competing). After confirming that athletic competition (track runners) resulted in lower CP ratings in both M and F athletes, they showed that, independently of athletic status, treadmill running produced analgesia in F but not in M, whereas sedentary video game competition had an analgesic effect in M but not in F. The authors, therefore, concluded that the components of competition-induced analgesia were different – that is, physical exercise in F and cognitive stress in M. However, these results reached statistical significance only with the CPT and not with the HP modality.

Koltyn et al. [111] compared the effects of maximal and submaximal isometric exercises on PP perception in F and M, and found a consistent analgesic response in the former group as expressed by significantly higher PTh and lower PInt after both types of exercise. In contrast, M only reported lower PInt after maximal isometric exercise. Hoeger Bement et al. [86] did not observe similar sex differences in the magnitude of exercise-induced analgesia after isometric contractions, but they argue that this type of analgesia may be dependent on the pain testing site as well as contraction intensity, as they did not study the same experimental parameters as Koltyn et al. [111].

Rhudy and Meagher [160] used loud noise to elicit stress-induced analgesia (SIA), and noted sex differences when the study subjects were submitted to radiant HP thereafter. Loud noise exposure resulted in decreased pain scores in F, whereas they were increased in M. The authors suggest that this differential effect appeared to be related to the emotional state elicited by noise, as they saw that F experienced fear and physiological arousal (SCL, HR) in response to noise, while M reacted only with surprise. Bragdon et al. [21] discerned no effect of a laboratory behavioural stress task on HP and IP sensitivity in both F and M. Similar results were obtained by al'Absi and Petersen [3] in response to a CP task after a public-speaking challenge or a standard condition. Quiton and Greenspan [155] examined the impact of a strong but not painful electrical stimulus (stress condition) on HP and did not observe any sex difference. However, when these same authors compared the effect of a mild but not painful electrical stimulus (distraction condition), they saw that the magnitude of the distraction-evoked hypoalgesia was significantly greater in M than in F for the sensory but not the affective dimension of pain.

Taken together, the results of the above studies indicate no clear sex difference in regard to stress-induced analgesia. Moreover, the strength of the analgesic response appears to vary according to stressor type and/or components of the stress experience, and may explain the variability of these findings.

3.1.6. Other biological factors needing further investigation

This section summarizes the results on the role of other biological factors for which 1 or 2 human laboratory studies are available (this sub-section focuses exclusively on laboratory studies that compared the role of these factors in F *and* M subjects). Kim et al. [110] and Fillingim et al. [59] examined whether thermal pain responses in healthy F and M were differentially affected by genes known to be involved in nociceptive transmission or opioid analgesia. However, it is difficult to derive helpful conclusions from these results, other than that research is promising in this field and further studies are needed. The same is true for the role of testosterone, although there is general consensus of its protective role in animals [6,7,39]. It is surprising that so little research has been done in the field of androgens considering that, compared to animals, humans have higher concentrations of these hormones, which are known to interact with a variety of neuroactive agents (eg, nerve growth factor, amino acids such as gamma aminobutyric acid, glutamate, and other neurotransmitters) that are themselves implicated in pain processing mechanisms at both the peripheral and central nervous system [7,38,39,41,63]. Between 1998 and 2008, only 1 laboratory study [107] with humans has been performed in this field, and inconclusive results were obtained.

Another understudied but promising area of research is the role of μ-opioid-mediated antinociception using brain imaging techniques in healthy F and M humans subjected to a painful stimulation. Zubieta et al. [208] conducted an elegant study in which they demonstrated significant sex differences in the magnitude and direction of the responses of the μ-opioid system in distinct brain areas following the application of an intensity-matched, deep painful stimulus. Smith et al. [177] also used a brain-imaging technique to compare the perceived intensity of deep pain in M and F in high- and low-estrogen conditions (see Section 3.1.1.1). F in the latter condition manifested significantly less regional activation of the endogenous opioid system, but the observed changes did not translate into significant sex differences in PInt.

Finally, we retrieved only one laboratory study [127] that examined sex differences in odour-induced modulation of pain. The results suggest that odours may affect HP perception in a sex-dependent manner, but it is premature to draw firm conclusions about this understudied mechanism.

3.2. Psychological factors

A large body of research between 1998 and 2008 examined the extent to which psychological factors may contribute to sex

differences in pain sensitivity. Considering the importance of depression and anxiety in chronic pain states [20,23,142,143,194], many laboratory pain studies have investigated the role of these factors in pain sensitivity in F and M. Several authors have focused on other possible cognitive mediators, such as pain catastrophizing and adaptive coping style.

3.2.1. Depression

Nine laboratory studies [1,28,66,106,147,156,160,173,201] investigated the interrelationships between sex, pain sensitivity, and depression. In a CPT experiment, al'Absi et al. [1] reported a positive correlation in M but not in F between McGill Pain Questionnaire (MPQ) ratings and scores on the depression subscale of the Profile of Mood State [129]. Using the Depression Anxiety Stress Scale [122], Keogh and Herdenfeldt [106] obtained the opposite result – that is, a positive correlation on the affective scale (but not on the sensory scale) of the MPQ-short form (SF) in F but not in M. Pinerua-Shuhaibar et al. [147] recruited healthy M and F subjects and then screened those who had minor depression to study sex difference in IP ratings. They observed that M and F had comparable pain responses in both the control and depressed groups. Wise et al. [201] noted that sex differences remained significant for PTh and PTol, but not for PUnp of HP after controlling statistically for the subjects' depression levels measured by the Beck Depression Inventory [15]. Carter et al. [28] investigated a paradigm in which they experimentally induced depression emotions and examined the effects on PP perception, taking into account the sex of the subjects. Both F and M assigned to this condition exhibited reduced PTol and reported greater PInt than those in the neutral condition. Except for 2 studies, all the others mentioned above failed to support a differential effect of depression on experimentally induced pain in F and M.

3.2.2. Anxiety/stress and anxiety sensitivity

The most commonly used instruments in laboratory research to assess dispositional or situational anxiety (or stress) include the State-Trait Anxiety Inventory (STAI) [180], the Anxiety subscale of the Profile of Mood State, the Depression Anxiety Stress Scale, the Stress Subscale of the Short Adjective Check List [126], the Stress Symptoms Rating Scale [136], the Perceived Stress Scale [35], the numerical rating scale, and the visual analogue scale.

To explore the relationship between experimental pain and anxiety/stress, several studies examined simple correlation coefficients in M and F and various pain outcomes (PTh, PTol, PInt, PUnp, sensory/affective scores, TS). al'Absi et al. [1], Quiton and Greenspan [156], Sarlani et al. [173], and Wise et al. [201] found no significant correlation between these pain outcomes and anxiety in both sexes. Other studies [65,95,97,98,178] reported a significant correlation between anxiety/stress levels and some pain measures in M but not in F, while Garofalo et al. [66] and Keogh and Herdenfeldt [106] obtained results in the opposite direction.

Similar inconsistencies were observed when authors employed more sophisticated statistics to analyze their results. Aslaksen et al. [10], Keogh et al. [102], Logan and Gedney [121], Robinson et al. [167], and Wise et al. [201] determined that sex was no longer a significant predictor of some pain responses when anxiety or stress levels were statistically controlled. However, sex remained a significant predictor of PTol in a study by Wise et al. [201], and Jones et al. [98] ascertained that when a CPT was performed, M who scored above the median on the STAI-Trait scale reported significantly greater PInt and PUnp and lower PTol than M scoring below the median; no such differences were detected between high- and low-anxious F. That anxiety seems to be a stronger predictor of pain in M was also illustrated by the observation that M with high-anxiety scores were comparable to low- and high-anxious F on all pain outcome measures. However, these authors failed to replicate their findings in a subsequent study except for the variable PTol [97]. (It should be noted that the only difference with the earlier study by Jones et al. [98] was that they categorized their participants as either being high- or low-anxious according to the State Scale rather than the Trait Scale of the STAI.) Experiments comparing pain perception and anxiety levels before and after maximal and submaximal isometric exercises disclosed no significant sex difference [86,111]. George et al. [73] also reported that STAI-State anxiety and sex were not significant predictors of CP Tol and Int (at Th and Tol). Jones et al. [98] obtained similar results with an HP stimulus. Finally, Campbell et al. [27] adopted a general linear model to examine the contribution of anxiety to sex differences in PInt and PUnp ratings of the IP test and did not find a significant interaction between these variables.

Other studies manipulated anxiety/stress to examine this effect on pain perception in M and F. Carter et al. [28] reported no significant sex differences in PTol and PInt with an emotion-induction technique in which subjects were requested to try to experience anxiety as suggested by a group of statements. Jones et al. [95] investigated the effects of anxiety-evoking instructions and found that only F in the anxiety condition had higher peak PInt scores than those in the neutral condition. When they compared both sexes in the anxiety condition, they observed that M had lower PTh than F, indicating again that anxiety could have a stronger effect on pain perception in M. Logan et al. [120] examined the effects of 3 experimental manipulations – cognitive/emotional stress, relaxation, and neutral video – and reported that F in the stress condition had greater PInt than their M counterparts.

Finally, a limited number of studies [97,102,103,189] paid specific attention to the concept of anxiety sensitivity (AS), which is defined as a trait tendency to experience fear of anxiety-related sensations (eg, palpitations, sweating), based on the belief that such symptoms are a sign of impending harm [159]. Two of these studies [97,102] observed a significant correlation between AS and pain sensitivity in M only. Opposite results were obtained by Keogh and Birkby [103] and Thompson et al. [189]. However, the results of both of these studies reached statistical significance on only one of the outcome measures (sensory subscale of the MPQ) and not on the other ones (PTh, PTol, and affective subscale).

In summary, several studies suggest that sex differences in experimental pain perception disappear when controlling for anxiety. However, inconsistent or contradictory results are obtained with regard to the direction of the association between anxiety within sex and across outcome measures.

3.2.3. Coping style

A good number of studies published between 1998 and 2008 examined whether M and F differ in their way of coping with pain during experimental nociceptive procedures. Specific attention was paid to the propensity to catastrophize and various types of adaptive coping strategies.

3.2.3.1. Pain catastrophizing. Catastrophizing connotes negative cognitive and emotional thoughts toward pain. According to Sullivan et al. [187], catastrophizing can be viewed as a concept that involves 3 related components: rumination, magnification, and helplessness. The 2 former components refer to appraisal processes where individuals focus on and exaggerate the threat value of a painful stimulus, while helplessness implies negative evaluation of the ability to deal effectively with pain.

Five studies [48,73,90–92,156] measured the overall propensity to catastrophize during different types of experimental pain procedures according to the Catastrophizing Subscale of the Coping Strategies Questionnaire [171]. These studies reported inconsistent patterns of results regarding the relationship between sex, catastrophizing, and pain perception. Quiton and Greenspan [156] and

Jackson et al. [92] found no significant correlations in either F or M between pain perception (HP Int and CP Tol) and tendency to catastrophize. Edwards et al. [48] noted that catastrophizing did not mediate the sex differences observed in experimental CP, HP, and IP Th and Tol. Jackson et al. [91] conducted a set of 2 studies in which they statistically controlled for catastrophizing levels, and obtained inconsistent results regarding the interaction between this variable and experimental CP responses in M and F. George et al. [73] undertook regression analysis to examine factors that could explain or contribute to CP Tol and Int (at Th and at Tol) and noted that catastrophizing did not significantly contribute to the observed sex differences in experimental pain perception.

Employing the Pain Catastrophizing Scale [187], Sullivan et al. [186] performed regression analysis to test mediational hypotheses, and observed that when the level of catastrophizing was controlled statistically, sex was no longer a significant predictor of CP Int (or duration of pain behaviours). Similarly, Weissmann-Fogel et al. [199] replicated these findings by showing that sex differences in DNICs were no longer significant after controlling for pain catastrophizing. Hirsh et al. [84] examined the relationship between sex, catastrophizing, and fear of pain before and after a CPT using hierarchical regression analyses, and found that sex was a significant predictor of PTol but not PTh and PInt. Pain-related fear explained a small but statistically significant variance in all 3 measures, while catastrophizing did not. Path analysis by Thorn et al. [190] determined that the differences between F and M in their responses to CP could be partially attributed to sex disparities in a more general masculinity-femininity personality trait (emotional vulnerability) (see Section 3.3.1). This factor acted as a better predictor of sex difference in pain responses than pre-CPT catastrophizing thinking. Path analysis by Dixon et al. [45] revealed that emotional vulnerability partially mediated sex differences in PTol, PInt, and PUnp through catastrophic thinking during the CPT.

In summary, the results of the above studies suggest that catastrophizing thinking may partially mediate sex differences in pain sensitivity, but this factor could itself be modulated by other psychosocial variables, such as personality trait.

3.2.3.2. Adaptive coping strategies. Various types of cognitive strategies can be adopted to manage pain. They include diverting attention, focusing on or reinterpreting pain sensations, coping self-statements, suppression of pain-related thoughts, and praying/hoping. Jackson et al. [92] and Thompson et al. [189] identified some sex differences in the repertoire of strategies used by M and F. They discerned that M tended to divert their attention in the presence of a pain stimulus, while F focused more on reinterpreting pain sensations. Jackson et al. [91], Quiton and Greenspan [156], and Sullivan et al. [186] failed to replicate these observations, but the experimental pain paradigms were different. Fillingim and Edwards [56] measured PP Th in M and F and type of coping strategies (active vs passive). They noted that passive coping was more common in F than in M. Separate multiple regression analyses for F and M revealed that active coping was a significant predictor of PTh in M, but passive coping did not explain a significant proportion of the variability in F PTh.

In a first study of a set of 2, Jackson [91] investigated experimental coping manipulation in which subjects had the opportunity to interact or not with an empathetic reflecting experimenter during a CPT (transaction vs no transaction). In the second study, the authors adopted the same experimental design but added 3 additional conditions in which the subjects were encouraged by the experimenter to (1) divert attention away from pain, (2) reinterpret painful sensations as neutral sensations, or (3) continue to tolerate the pain. As expected, F had lower PTol levels than M, but were not more likely to engage in interpersonal transactions with the experimenter. However, when F did, they were found to be more pain-focused in their interactions than M (Study 1). In study 2, F were encouraged by the experimenter to use adaptive coping strategies and they exhibited greater PTol compared to conditions in which they were not given this opportunity. Interestingly, their PTol levels were comparable or exceeded those observed in M in the same conditions. In a more recent study, Jackson [90] added an additional condition to the above experimental design in which the experimenter magnified the negative affective aspects of pain. The results showed that PTol in M were not influenced by the different conditions, while the F were influenced. Taken together, these results suggest that the nature of interpersonal interactions with the experimenter may have a greater influence in F than in M on pain coping and tolerance.

In a series of recent studies, Keogh et al. [102,104–106] examined the effects of different types of coping instructions on experimentally induced pain in M and F. When subjects were instructed to either pay attention to a CP stimulus or to avoid it, no sex effect was evident for all pain responses (eg, PTh, PTol, PInt) [105]. In a subsequent study [106], subjects were instructed to focus specifically on the sensory or affective components of the CP stimulus. Sensory focusing had a beneficial effect only in M (lower sensory MPQ-SF scores, higher PTh and PTol). In contrast, emotional focusing had a negative effect in F, although this was true only for affective MPQ-SF scores. In a similar experimental paradigm where subjects were asked to either accept pain or try to control it (acceptance-based vs control-based coping), Keogh et al. [104] observed that the former type of instructions reduced affective CP scores in F only. However, results did not reach statistical significance in any other pain measures, and Keogh et al. failed to replicate their findings in a subsequent study [102].

Mitchell et al. [131] tested 3 types of distraction strategies in M and F during an experimental CP procedure. The condition included an arithmetic task, an audiotaped comedy show, or a musical choice selected by participants. They observed no interaction between sex and the type of distraction used for CP Tol or Int. Kenntner-Mabiala et al. [101] also were interested in the attentional focus principle in M and F who were submitted to an experimental PP task. Subjects were asked to focus either on (1) pictures (positive, negative, neutral), (2) sensory pain, or (3) affective pain. Their results showed significant sex differences, where F in the picture-focusing group reported lower PInt compared to those in the affective pain group. No significant attentional effect on pain perception was noted in M. Another study by Kenntner-Mabiala et al. [100] investigated whether changes in tempo and mode of classical music could affect HP perception in both sexes. They observed that F but not M exhibited higher PInt and PUnp ratings according to the fast music tempo compared to slow music tempo.

In conclusion, coping style seems to contribute to sex differences in an experimentally induced pain task. Several studies suggest that F tend to cope better with pain when they employ pain attentional focus or reinterpreting pain sensation strategies, whereas distraction may be more efficient in M. There is also some evidence that the nature of the interpersonal interactions with the experimenter could have a positive influence on PTol in F but not in M.

3.3. Social factors

3.3.1. Gender-specific beliefs/expectations and perceived self-efficacy

Gender-specific beliefs and expectations about pain, which are partly acquired through social learning, have been proposed to act as potential factors contributing to differences in pain perception in F and M. Gender role broadly refers to a socially accepted set of characteristics ascribed to each sex. With regard to pain, feminine role is stereotypically associated with greater willingness to report pain, whereas the expected masculine role is more related to stoicism [51]. Between 1998 and 2008, 13 studies

[45,54,113,123,135,137,149,163,166,167,172,190,201] used questionnaires, video observations, or laboratory manipulations to investigate the relationship between gender role and pain experience in M and F subjects.

With the Bem Sex Role Inventory [16], a measure of gender-related personality trait (masculinity–femininity), Myers et al. [135] found, in a set of hierarchical regression analyses, that sex was a predictor of CP Th, while gender role or interaction term (gender role by sex) did not explain a significant proportion of the variation on this measure. For PTol, they observed that when gender role was first entered into the model, both sex and gender role were significant independent predictors. However, when gender role was entered second in the regression, its contribution was no longer statistically significant (neither was interaction term), suggesting that gender role socialization did not independently explain the sex differences seen in CP Tol.

Sanford et al. [172] adopted the Extended Personal Attributes Questionnaire (EPAQ) [179] to assess positive and negative masculinity-femininity traits. M and F were found to differ significantly on only 1 of the EPAQ subscales (positive feminine gender role). When the scores obtained on this scale were entered into a regression analysis model in combination with pain appraised as a threat (as opposed to a challenge), sex was no longer a significant predictor of CP Tol, indicating that these 2 factors may partly mediate the relationship between sex and PTol. Two other studies [45,190] tested a path analytical model to investigate whether the gender role personality trait (standard or modified version of the EPAQ) contributes to or mediates the relationship between CP and sex. Both studies determined that the masculinity-femininity scale was a significant predictor in their model, but in a different manner. It is noteworthy that lower scores on the masculinity-femininity scale are thought to indicate emotional vulnerability, whereas higher scores signify emotional stability. Thorn et al. [190] reported that emotional vulnerability was a central mediating factor in the sex differences in CP Tol and Int. On the other hand, Dixon et al. [45] observed that emotional vulnerability acted as an indirect mediator through catastrophizing (see Section 3.2.4.1) to predict sex differences in CP Tol, Int, and Unp.

Another questionnaire that assesses subjects' views of typical M and F with respect to pain sensitivity, pain endurance, and willingness to report pain is the Gender Role Expectations of Pain [165]. Wise et al. [201] and Robinson et al. [167] used the "stereotypical willingness to report pain" scale in their regression model and obtained similar results. Wise et al. [201] found that when gender role was controlled for, sex was no longer a significant predictor of PTh and PUnp, but remained significant for PTol (6% of variance). Robinson et al. [167] examined the gender role influence on TS in M and F. Their results also showed that sex was no longer a significant predictor of TS magnitude when stereotypical willingness to report pain and anxiety (see Section 3.2.2) was entered into a regression model. Pool et al. [149] (study 2) recently examined an EP task in M and F who scored in the top and bottom third on the gender group identification subscale, that is, "ideal men" or "ideal women." These authors observed that only high-identifying M (top third) presented greater PTol (but not PTh) compared to low-identifying M (bottom third) or F (top and bottom third).

Nayak et al. [137] investigated beliefs about appropriate pain responses in same-sex subjects in relation to CP in F and M. The results of regression analyses indicated that gender beliefs about appropriate pain responses, sex (M or F), and culture (India or USA) were not significant predictors of PInt. For PTol, sex and culture were not significant predictors, whereas PInt accounted for a majority of variance, and beliefs about appropriate pain responses predicted an additional small (5%) proportion of variance, suggesting that when participants considered pain expression to be less appropriate, they exhibited higher PTol. Kunz et al. [113] examined whether M and F differed according to their facial expressions when they were submitted to an HP task. These authors did not find significant sex differences for HP perception. They reported that both M and F were comparable with regard to facial expression of pain during an HP task. The same was true for self-reported PInt. Robinson et al. [163] gave different sets of instructions to manipulate gender role performance expectations. During a CPT, subjects were either told that (1) a typical M/F could tolerate pain for 30 s, or (2) lasting time was 90 s for a typical M/F, or (3) they received no information about performance. In the latter condition, M were reported to have higher PTol and lower PInt than F. Moreover, this difference in pain perception disappeared when they received information about expected performance (30 or 90 s). Fillingim et al. [54] gave another set of instructions to manipulate gender-related perceived ability to tolerate IP. Prior to the pain task, when M subjects were told that F would tolerate more pain because of their autonomic nervous system (feminine condition), they exhibited higher PTol compared to their M counterparts who were told the opposite (masculine condition) or to F, irrespective of the instructions they were given. However, these sex differences were noted only for PTol. When the association between self-reporting and PTol was examined, they found that for M in the feminine condition, motivation was positively correlated with higher PTol to IP at post-task.

Lowery et al. [123] suggested that motivation could act as a mediating factor between gender role expectancies and PTol. They hypothesized that monetary incentive manipulation would produce greater effects among F than M subjects because the latter group has higher endogenous motivation with respect to the demands of stereotypical M gender role. No main effects or interactions with monetary incentive instructions were detected for CP Th, Tol, or MPQ ratings in either sex. The only significant observation was PInt at pain tolerance level, where M in the high-incentive condition had lower ratings than those in the low-incentive condition; the opposite pattern was noted for F.

In light of the above studies, it is reasonable to conclude that gender role expectancies probably play a significant role, explaining some of the differences in experimental pain perception in F and M. Masculinity-femininity trait (eg, emotional vulnerability) and perceived identification according to typical M/F stereotypes (eg, willingness to report pain) seem to alter PTol, PInt, and PUnp.

Other authors examined whether perceived self-efficacy, a concept conceptually linked to gender-specific beliefs/expectations, may contribute to explain sex differences in experimental pain perception. The concept of self-efficacy, which may be, at least in part, influenced by social factors, is defined as a general expectation that one can successfully perform behaviours necessary to produce a successful outcome [13]. Jones and Zachariae [97] did not find a significant sex difference in the correlation between efficacy/control beliefs and CP responses. Jackson et al. [92] measured perceived physical self-efficacy (ie, expectations about one's overall physical capabilities) and task-specific efficacy (ie, beliefs about one's abilities to cope successfully with an upcoming painful stimulation) and found that F reported significantly lower levels of perceived self-efficacy, reduced PTol to CP, and increased PInt. After controlling for self-efficacy beliefs, sex was no longer a significant predictor of PTol and PInt.

Goldberg et al. [76] manipulated perceived self-efficacy by creating a cognitive set of success or failure aimed at influencing subsequent CP responsiveness and found that experiencing success did not influence pain perception in F, while it increased PTol and reduced PInt ratings in M. In contrast, experiencing failure augmented PTol in F and PInt in M, indicating that F may react differently to success/failure than M. However, the results of this study must be interpreted with caution due to some questionable methodological issues. Considering the relatively small number of

studies in this field, more research is needed to elucidate the role of perceived self-efficacy in the way women and men react to pain.

3.3.2. Experimenter sex

As mentioned previously, M and F evolve in a social context endorsing "stereotypical" roles according to their sex. As a result, both M and F may display different responses towards a painful stimulus, depending on the sex of the experimenter who runs the experimental session. This issue was examined by analysis of variance (and/or multivariate analysis of variance) in a total of 13 recent studies. The results on most outcomes suggest no significant interaction between experimenters' and participants' sex for PTh [50,54,57,99], PTol [28,54,57,91,190], PInt [28,54,75,91,99,190, 198], and PUnp [10,54,190,198]. Kallai et al. [99] also investigated the possible interaction between participants' sex and professional status (low vs high) of the experimenter, and did not find a significant difference on any pain sensitivity measures.

In contrast, Gijsbers and Nicholson [75] observed that M showed significantly higher mean PP Th when they were tested by an F compared to a M experimenter, whereas no such difference was seen in F. On the other hand, Kallai et al. [99] reported that both M and F participants had higher CP Tol when they were tested by an experimenter of the opposite sex. Sternberg et al. [183] obtained similar results in F subjects only for CP Int and Unp, whereas they recorded lower pain responses when tested by an experimenter of the opposite sex (it is noteworthy that because of the imbalance of experimenter sex, Sternberg et al. [183] conducted their analysis only in women with athletic status who were compared to M [athletes and nonathletes]. Also, their sample size was relatively small). Aslaksen et al. [10] also observed that only M who were tested by an F experimenter showed less HP Int. These authors conducted a second set of multiple regression analysis and found that the interaction term "M subjects" by "F experimenters" was a significant predictor of PInt but not PUnp.

An interesting study by Braid and Cahusac [22] examined whether pain responses vary according to sex when another participant of the same or opposite sex applied a PP algometer on their sternum. Their results also showed no significant interaction between the subjects' and the administrators' sex for either PP Th or Tol. Brown et al. [24] failed to discern a significant difference regarding CP ratings between M and F who were supported by a friend or by a stranger when the task was administered. The authors also examined sex differences according to the kind of support received (active, passive, or limited interaction) and again, there was no significant interaction. McClelland and McCubbin [128] administered the MPQ-SF to M and F who were accompanied or not by a same-sex friend on a CP task. Their results showed a significant interaction, where F with a same-sex friend present during the experimental pain task reported significantly greater PInt compared to those who were alone. The results were in the opposite direction for M. These authors also suggested that F participants with a same-sex friend reported higher affective pain ratings compared to M participants with a same-sex friend.

In summary, the actual literature does not clearly support experimenter sex as a possible factor that could explain sex differences in experimentally induced pain. However, studies that did report some differences in M and/or F participants seemed to agree that subjects were performing better (ie, had higher PTol or lower mean PInt) on a laboratory pain task when they were tested by an experimenter of the opposite sex. There is actually no clear evidence regarding the influence of supportive others in M and F responsiveness to pain.

3.4. Past history

Very little research has investigated the role of familial pain models, history of childhood sexual and/or physical abuse, and recent pain episodes reported by healthy M and F undergoing an experimental pain task, but this could be relevant from a clinical point of view.

Fillingim et al. [57] examined the relationship between HP and numbers of clinical pain episodes reported by healthy M and F over the past month. They found that F who reported higher levels of clinical pain had lower PTh and PTol compared to their F counterparts, while no such differences were observed in M. Hellström and Lundberg [82] explored the relationship between CP Th and frequencies of common pain symptoms (headache, neck or shoulder pain, and back pain). They also found that F who reported more frequent pain symptoms exhibited lower PTh than those with less pain episodes. No such relationship was noted for M.

To our knowledge, Fillingim et al. [58] performed the only study between 1998 and 2008 that examined sex differences in experimental pain perception and familial pain. In this study, subjects with a family history of at least 2 types of pain (rather than measured by number of family members) were considered to have a positive familial history (FH+) of pain. The authors detected a significant interaction where F with FH+ had lower HP Th and PTol than F with FH−; no difference emerged in M subjects. Fillingim and Edwards [56] investigated the possible influence of history of childhood sexual and/or physical abuse in sex-related experimental pain responses. Their results showed no significant interaction between sex and history of abuse for IP and HP perception. However, for TS of HP, they observed that F with a positive history of abuse reported lower PInt (at 52 °C) and lower PUnp (at 49 °C and 52 °C) than those with no history of abuse, suggesting a decrease in pain sensitivity in the former group. No such difference was seen between the 2 groups of M or on any pain measures.

In summary, some experimental evidence suggests that individual past history may influence pain perception in F but not in M. However, the literature needs to be enriched before drawing any strong conclusion about the importance of past life experiences as a possible mediating factor in the relationship between experimentally induced pain and sex.

4. Discussion

Between 1998 and 2008, more than 125 laboratory studies examined the role of various biopsychosocial factors in sex/gender differences in experimentally induced pain perception. We conducted a comprehensive systematic review of the literature on this subject, and our results can be summarized as follows:

Biological factors: The experimental evidence that genetic, hormonal (estrogens, androgens, stress hormone) and physiological factors (BP regulation, HR, and electrodermal reactivity) may contribute to sex differences in pain sensitivity in healthy subjects is either of small magnitude, insufficient, inconsistent, or absent. Among peripheral and CNS mechanisms, some studies suggest that the phenomena of TS of pain, allodynia, and secondary hyperalgesia could be more pronounced in F than in M, which might indicate that central sensitization is augmented in healthy F. Other mechanisms, such as peripheral sensitization and SS of pain, do not appear to be involved. Although many studies have tested the hypothesis that endogenous pain inhibitory systems (DNICs, SIA) could be less efficient in F than in M, the experimental evidence to support it is mixed and does not necessarily apply to all pain modalities.

Psychological factors: It does not appear that depression mediates some of the observed sex differences in experimental pain perception, while the role of anxiety is ambiguous. With regard to anxiety or AS, inconsistent and contradictory results are reported about the direction of the association between these

factors and pain sensitivity within sex. With regard to coping style, catastrophizing could partially mediate sex differences in pain sensitivity, but more important psychosocial variables, such as masculinity–femininity personality trait, may also be involved. Adaptive coping strategies also seem to have a significant role, where F may cope better with laboratory pain when they are using pain attentional focus or reinterpreting pain sensations strategies, while distraction may be more efficient in M. There is also some evidence that the nature of the interpersonal interactions may exert a greater positive influence on pain coping and tolerance in F than in M.

Social factors and past history: Manipulation of gender expectations seems to influence experimental pain perception in both F and M. It is reasonable to conclude that gender role expectancies, masculinity–femininity trait (eg, emotional vulnerability), and perceived identification according to typical M/F stereotypes (eg, willingness to report pain) may each explain, at least partly, sex-related differences in pain sensitivity. No clear evidence supports a central role of experimenter sex in differences between F and M. When this is the case, there is some agreement that healthy subjects perform better (eg, higher PTol, lower PInt) if they are tested by an experimenter of the opposite sex. Finally, some experimental evidence indicates that past history (recent pain episodes, familial pain model, history of childhood sexual abuse) may influence pain sensitivity in F but not in M, although the results are not consistent on all outcome measures.

The above conclusions must be treated with much circumspection for the following reasons. Firstly, some studies (eg, [31,83,125,177,207,208]) were successful in identifying certain explanatory factors and/or underlying mechanisms, but their findings did not translate into significant sex differences in pain responses (eg, F = M for PInt). Secondly, many studies reported statistically significant sex differences in pain sensitivity, but these differences were often of a small magnitude and were not necessarily significant across all pain modalities (eg, CP, HP, PP, IP, EP), tested body sites, and/or outcome measures (PTh, PTol, PInt, PUnp). Thirdly, it is important to consider that when sophisticated models of statistical analysis are used to assess the relative contributions of various factors, the percentage of explained variance remains very small. In such a context, the relevance of some of the observed results may be viewed as questionable, not only from an experimental but also from a clinical point of view. Finally, the available findings for some of the hypothesized factors/mechanisms are based on only a very small number of studies with limited sample sizes and/or divergent methods so that it is very difficult, if not impossible, to derive reliable and useful conclusions. In light of all these considerations, it is not surprising that the effects of some biopsychosocial factors are inconsistent, minimal, or absent.

Some of our conclusions are somewhat different from those published recently by Fillingim et al. [60]. One of the reasons might be that we took a systematic approach to reviewing the literature. We also chose to restrict our review to only studies involving both healthy F and M to summarize the research in this field. Finally, we applied a thorough methodology to critically examine the role of biopsychosocial factors in sex-related differences in experimental pain. Popescu et al. [150] recently published an excellent systematic review of the literature on sex differences in pain modulation by DNICs in which they statistically quantified the range of observed differences. As mentioned before, it was not possible to adopt a similar approach due to the large number of factors/mechanisms that we wished to cover in the present review. Nevertheless, our conclusions about sex-related differences in DNIC modulation are not that different from those of Popescu et al. [150].

As mentioned in our companion paper published in the previous issue of *Pain*® [157], the present article has some limitations. Our search was limited to the English language, which may have led to a bias against publications in other languages and thereby restrains the generalizability of our conclusions to different cultural groups. It is also important to note that potentially relevant articles may have been excluded if they did not expressly contain the terms "pain," "sex," "gender," "males," "men," "females," and "women" in their abstract/subject headings/title. However, the present systematic review included more studies than any previously published papers and this can be seen as a strength.

Despite the limitations of the present systematic literature review, our results raise several important questions. In the mid-1990s, 3 important papers [17,61,194] paved the way for an entire series of studies on sex/gender variations in pain perception. Between 1998 and 2008, we retrieved 129 studies on the role of biopsychosocial factors, and a plethora of review papers has been published since then [6,7,14,18,19,25,37–39,41,52,53,60,63,87,96,130,134,140,150,161,162,168,176,195,200]. What have we learned in these 10 years of laboratory research? There is no doubt that innovative human experimental models that better mimic clinical pain have been developed, and contributed to increasing our knowledge in the field. Furthermore, some factors/mechanisms that may contribute to sex differences in healthy subjects remain understudied (eg, genetic factors, opioid receptor-mediated nociception) and certainly merit further investigation using stimuli that induce deep, tonic, and relatively long-lasting pain (eg, capsaicin, glutamate, hypertonic saline, ischemic pain). The number of studies that used neuroimaging techniques is also very small, and this methodology offers a promising research avenue. However, when we consider the overall quantity of studies that have been done in the field, it remains that the sum of *really new knowledge* that has been generated over this decade is rather restricted. More importantly, the clinical impact of all the results of these laboratory studies is somewhat limited. In fact, it could be argued that we are still very late in identifying the biopsychosocial factors that explain sex differences in clinical pain states and how they may impact on analgesic treatment in women and men.

In light of the above considerations, we can question ourselves about the relevance of pursuing research on healthy subjects, at least in some areas. If we do so, we must refine and standardize our experimental models to avoid methodological disparities, assure high quality paradigms, and ensure a greater likelihood of translating the findings to the clinic. More studies should also be done in pain centers and community settings to assess whether (and to what degree) findings from laboratory studies in university students of young age support those obtained in patient populations that suffer from acute or chronic pain of different origins. In our companion paper [157], we discussed several methodological issues, and we made the 4 following recommendations and suggestions for future research: (1) laboratory studies on sex-related differences in pain perception should be performed not only on healthy volunteers of various ages but also on participants with painful pathologies, (2) primary and secondary outcomes should be defined beforehand, (3) sample size should be estimated as a function of primary outcome and an effect size of clinical significance, and (4) standardized and more uniform testing procedures need to be adopted. However, it is clear that other avenues must also be explored.

4.1. Conclusion

The results of our systematic literature review suggest that pain sensitivity in healthy F and M could be altered differently by some biopsychosocial factors. However, this conclusion must be treated with circumspection for various methodological reasons. Although

some areas remain understudied in this field of research, there is a need to assess and improve the ecological validity of findings from laboratory studies on healthy subjects, and perhaps a change of paradigm needs to be considered at this point in time to better understand the factors/mechanisms that influence the experience of women and men who suffer from acute or chronic pain.

Conflict of interest statement

The authors report no conflict of interest.

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