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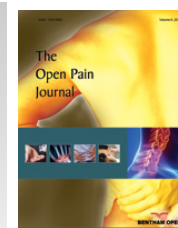
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## REVIEW ARTICLE

# Effect of Age, Sex and Gender on Pain Sensitivity: A Narrative Review

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### Abstract:

#### Introduction:

An increasing body of literature on sex and gender differences in pain sensitivity has been accumulated in recent years. There is also evidence from epidemiological research that painful conditions are more prevalent in older people. The aim of this narrative review is to critically appraise the relevant literature investigating the presence of age and sex differences in clinical and experimental pain conditions.

#### Methods:

A scoping search of the literature identifying relevant peer reviewed articles was conducted on May 2016. Information and evidence from the key articles were narratively described and data was quantitatively synthesised to identify gaps of knowledge in the research literature concerning age and sex differences in pain responses.

#### Results:

This critical appraisal of the literature suggests that the results of the experimental and clinical studies regarding age and sex differences in pain contain some contradictions as far as age differences in pain are concerned. While data from the clinical studies are more consistent and seem to point towards the fact that chronic pain prevalence increases in the elderly findings from the experimental studies on the other hand were inconsistent, with pain threshold increasing with age in some studies and decreasing with age in others.

#### Conclusion:

There is a need for further research using the latest advanced quantitative sensory testing protocols to measure the function of small nerve fibres that are involved in nociception and pain sensitivity across the human life span.

#### Implications:

Findings from these studies should feed into and inform evidence emerging from other types of studies (e.g. brain imaging technique and psychometrics) suggesting that pain in the older humans may have unique characteristics that affect how old patients respond to intervention.

**Keywords:** Age, Sex, Gender, Pain sensitivity, Experimental pain.

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## 1. INTRODUCTION

Age and sex are the main non-modifiable [i.e. cannot be changed] biological factors that affect pain. An increasing body of literature on sex and gender differences in pain sensitivity has been accumulated in recent years. There is also evidence from epidemiological research that painful conditions are more prevalent in older people [1, 2]. Nevertheless, there were few studies that have investigated sex and gender differences throughout the life span [3, 4] and even fewer that have investigated experimental pain sensitivity in older age groups mainly because of challenges in recruiting older healthy pain-free individuals to examine their pain responses in a laboratory [2, 5, 6]. The evidence from experimental pain studies about the effect of age is also complicated by the fact of the complexity of pain in older adults and by the existence of other co-morbidities. In contrast, there are several studies that have reached a consensus regarding sex and gender differences in pain sensitivity [7 - 10].

Growing evidence suggests that experience of pain is influenced by genotype [11], ethnic characteristics [12], and psychological factors such as anxiety and catastrophising [9]. The age of an individual is also an important factor that affects pain, although there has been relatively little research conducted to date [13 - 15]. If the underlying causes of the individual differences in pain sensitivity response, including age, are well understood, then the treatment and management approach can be specifically tailored for each individual in order to achieve better pain relief. Individualized treatment and management can be affected at different levels including the choice of type and dosage of analgesic medication, choice of non-drug adjuvants and the approach taken to pain education. For example, elderly individuals might need re-enforced advice and more additional care and support than younger people. Moreover, techniques used for assessment differ according to age. For example, the tools and techniques used to glean present pain intensity ratings differ between young children and elderly individuals with comorbidities such as dementia.

It has been found that age may influence an individual's experience of pain [13 - 15]. It has been consistently documented that there is a positive linear relationship between age and chronic pain experience [16]. However, the findings of experimental studies are inconsistent, with some experimental studies showing an increase in pain sensitivity with increasing age, while others found no pain differences between different age groups [15, 17]. Reasons for these inconsistencies include methodological differences between studies, such as the size and type of samples, and the experimental pain techniques employed including the type of stimulus used. Most studies used only one experimental pain induction method and did not compare pain sensitivity response to different types of stimuli [15]. Hence, there is a need for future research to carefully examine pain sensitivity responses using different pain induction techniques within the same group of study participants.

In the last two decades a rapidly growing body of literature on the relationship and mechanisms contributing to variation in pain sensitivity according to sex/gender was published [for reviews see [7, 18]]. Evidence, from this literature, suggests that there are differences between males and females in the way they report their pain in both experimental and clinical situations [7, 19, 20]. The sex differences in reporting of pain in clinical situations are more consistent than sex differences in reporting of pain sensitivity observed in studies exposing healthy humans to experimentally induced pain [8, 9, 21].

The aim of this narrative review is to critically appraise the relevant literature investigating the presence of age and sex differences in clinical and experimental pain conditions to identify gaps of knowledge in the research literature and suggest a strategy for future research concerning the effect of age on pain responses.

### 1.2. Age Differences in Pain

It has been suggested that the age variable has an effect on pain perception and can explain most of the differences associated with pain [13, 15, 17].

#### 1.2.1. Age Differences in Clinical Pain

There is a consistent positive linear relationship between age and experience of chronic pain [16]. Numerous reviews suggested that an increased frequency, severity, impact, and anatomic distribution of persistent pain have been associated with older aged individuals [2, 22 - 24]. There is, also, an age-related increase in the prevalence of arthritis [25], fibromyalgia [26] and trigeminal neuralgia [27]. This might be due to poor quality of life and increased probability of physical disability in older people [28]. Although almost all findings in the clinical literature are consistently pointed towards an increase in clinical pain with age [2, 24, 29, 30], the effects of aging on pain perception remain unclear [16].

### **1.2.2. Age Differences in Experimental Pain**

In comparison with data from clinical studies, experimental data on the influence of age on pain are relatively inconsistent and contradictory [15, 17]. For example, while decreased pain thresholds in the elderly have been reported in studies using mechanical pressure [15, 31] and ischemic pain stimuli [32] pain thresholds to electrical stimuli seem to be relatively unchanged [17] and pain thresholds to thermal stimuli, with few exceptions *e.g.* [33] appear to increase with aging [34 - 38]. This suggests that the pain induction method chosen is one possible source of this inconsistency. To overcome this problem, a multimodal sensory testing method is needed in future research to widely examine the effect of age on pain experience. In addition, responses to experimental pain stimuli are found to differ according to the site of nociceptors stimulated, duration of the stimulus, quality of noxious sensation tested, and type of nerve fibre stimulated [32]. Accordingly, the effects of these variables on the findings could be reduced, and the limitations of the experiments could be overcome, by examining pain sensitivity responses between different age groups of participants by stimulating the same body site using similar settings.

### **1.2.3. Physiological Changes with Aging**

Aging is usually associated with changes in pain perception, including chronic pain occurrence and pain threshold modification [39]. Aging can be described as a dynamic process in which there are changes and compensations in the structure and function of different physiological and psychological components, including anatomical structures involved in the sensation of pain [6]. There is some debate in the literature about the occurrence of physiological alteration in the processing of nociception and pain, which can be ascribed to age [2, 40, 41]. It is clearly evident that there is a high prevalence of chronic pain in the elderly, and this can be attributed partly to the physiological changes of peripheral and central [38]; pain mechanisms and to changes in some psychological attitudes towards pain [41]. It has been reported that changes in sensations and perceptions in sensory systems occur in the elderly [42]. These perceptual changes, which reflect some overall nervous system changes, are not specifically due to changes of sensory modalities.

A large amount of the literature on the neurobiology of aging suggests that there is a widespread and considerable alteration in the structure, function, and biochemistry of the peripheral [13, 37, 38] and central nervous system [13] structures of older individuals. It has been documented that there is a decrease in the density of myelinated fibres with aging [43 - 45]. In contrast, some studies have found a decrease in the density of unmyelinated fibres [43, 46], whereas others did not report these changes [47, 48]. It has been recognized that myelinated fibres tend to show more decline in density [43] and function [49] than unmyelinated fibres, as well as decreased nerve conduction velocity and structural modifications in the elderly [38, 44]. Furthermore, it has been suggested that aging processes affect myelinated A delta fibre, but unmyelinated C- fibre appear to be less affected or unaltered [39].

In addition, there is a marked increase in the number of sensory fibres with signs of damage or degeneration, both myelinated and unmyelinated, with advancing age [38, 44, 50]. Aging is found to affect some functional and morphological features of the peripheral nervous system [38]. However, morphological studies have revealed a loss of unmyelinated and myelinated nerve fibres in old people, and some other abnormalities affecting mainly myelinated fibres, such as remyelination, demyelination, and appearance of myelin balloon figures. This deterioration, frequently seen in aged nerves myelin sheaths, may be explained by a decline in the major myelin proteins expression (P0, PMP22, MBP). Axonal atrophy of aged nerve fibres may be owed to a decrease in the expression and axonal transport of cytoskeletal proteins in the peripheral nerve fibre. This may explain some age related differences in pain sensitivity responses using different modalities because different noxious stimuli are found to activate different types of nerve fibres. With aging, there is a slowing in nerve conduction velocity which may result in reduced responses to tactile stimuli and pain perception alteration [38, 42]. In addition, it has been found that in old people, there is a decrease in nerve related body performance [51], and general reduction in neural efficiency, which results in decreasing the capacity of each neural unit [51, 52].

It has also been suggested that there is an extensive degenerative alteration in the spinal dorsal horn sensory neurons of aged subjects [13, 53]. In addition, structural and physiological aging-related changes of many brain regions were reported [51]. The prefrontal cortex, particularly catecholaminergic inputs, is found to be one of the most strongly affected brain regions [54, 55]. Changes like loss of dendritic arborisation, neuronal death, and neurofibrillary abnormalities are found to occur in the cerebral cortex of aging individuals, including areas which are involved in nociceptive processing, like the prefrontal cortex, primary and secondary somatosensory cortex, anterior cingulate, hippocampus, thalamus, and insula [13]. The turnover and concentration of catecholamines [56] GABA [57] and opioid receptors [58] within the limbic system are found to be decreased, as well as serotonin receptor density [59], mainly

within the prefrontal cortex and anterior cingulate [60].

It was evident from several biochemical studies that the content of substance P is found to be markedly decreased in the skin of aged people [61] and there is also an evidence of a decline in the rate of CGRP axonal transport with aging [62]. Substance P and CGRP are known to be major neurotransmitters of primary afferent nociceptive fibres, and therefore reduction in the content of neuropeptides might reflect a decrease in the nociceptive nerve density or functional integrity [13]. These findings suggest the presence of lesions and dysfunction in primary afferent sensory neurons in the elderly.

It has also been documented that there is a decrease in the function of the pain inhibitory system with aging [13]. Similarly, it has been found that reduced endogenous pain inhibition is noticed more in older adults compared to younger people [6]. The decreased endogenous analgesic system efficacy is probably expected to cause more severe pain succeeding prolonged noxious stimuli [13].

A growing body of literature on cognitive function in the elderly suggests that there are deficits in multiple cognitive domains in aged adults including executive function, episodic memory, attention, inhibition, and working memory [51, 63]. Moreover, it has been reported that with normal aging there are some working memory capacity limitations, decline in psychomotor skills, and slowing in the speed of processing [42]. The structural, molecular, and cellular changes associated with the aging process result in extensive reduction in neural and metabolic efficiency and this might probably be the cause of capacity limitations in the elderly [51, 64].

There is also an evidence from both animal and human studies that Hypothalamic-Pituitary-Adrenal axis activity contributes to biological aging by affecting glucocorticoid secretion and altering the synthesis of regulatory peptides and ultimately affecting the processing of pain experience.

### **1.3. Sex Differences in Pain**

To comprehend the differences between males and females in pain sensitivity response, it is important first to discuss the differences between the terms sex and gender and their relationship to each other, which will hopefully provide the theoretical basis for the precise use of each term.

#### ***1.3.1. Distinguishing Between Sex and Gender***

The terms sex and gender are often used interchangeably in conversation. The World Health Organization (WHO, 2014) defines sex as “the biological and psychological aspects of men and women” and defines gender as “the socially built characters, behaviours, and events that a given society reflects which is suitable for each one of men and women”. Clearly, characteristics of gender might differ considerably between communities and societies.

Sex is referred to as the way by which organisms are classified on the basis of their reproductive systems and the chromosomal complement allocated functions. Gender on the other hand is a self-representation of the individual as a male or female, or how the social institution will respond to that individual on the basis of gender presentation of the individual [65]. It has been reported by Greenspan that the term “gender differences” should be used if the gender is exactly debated [9]. In this narrative review the terms sex differences or sex/ gender differences will be, mostly interchangeably, used to indicate that sex/gender are being used as indicators, not as a reference to biological aetiology as argued by Deaux [66] or self-representation of an individual as male or female as argued by Wizemann and Pardue [65]. Though, in many situations when it is difficult to determine which term is accountable for the differences, and because, as it has been reported that gender is mostly ascertained by sex of the person, the terms sex or sex/gender will be used [10].

The effect of sex and gender on pain has recently been discussed as an important topic by many researchers. Most of the previous clinical and experimental studies have found that males and females differ in their experience of pain [7].

#### ***1.3.2. Sex Differences in Clinical Pain***

There is a higher prevalence of certain painful conditions in females including temporomandibular joint disorder [67], Fibromyalgia [7, 21], and headaches and migraines [68]. Overall, women are more likely to experience chronic pain [7], present with pain at multiple sites [21] and be more immobilised by pain than men [69].

#### ***1.3.3. Sex Differences in Experimental Pain***

Females have been found to have higher pain sensitivity responses than males [70]. Evidence suggests that females

report lower pain thresholds and pain tolerances and higher pain intensity to experimental pain than males [7]. It is also claimed that in the same pain conditions, females experience more severe, anatomically diffused, and long lasting experimental pain than males, although evidence is not as strong [71]. Moreover, a review of experimental studies by Racine *et al.* (2012) found that sex differences in response to experimental pain were not consistent in all studies [72]. Thus, there appears to be more consistency in sex differences in clinical pain studies than experimental studies. Nevertheless, although some researchers found that females seem to be more sensitive to both clinical and experimental pain as compared to males, some other researchers presented no difference. Differences in pain sensitivity response between males and females could be influenced by many factors.

#### **1.3.4. Factors Affecting Sex Differences in Pain**

Biological, psychological, and social factors influence sex differences in pain response. Experimenter appearance and possible personal biases might also have an effect [73].

##### **1.3.4.1. Biological Mechanisms**

To understand the differences between males and females in pain experience, it is important to know the effect of sex hormones. As sex hormones are found to fluctuate along the menstrual cycle in females, some investigators interpreted the presence of sex differences to pain owing to the influence of gonadal hormones [74]. There are two main gonadal hormones [sex hormones] in females, oestrogen and progesterone, and the levels of these two hormones varies across the menstrual cycle. Physiologically, the menstrual cycle is divided into three stages: the follicular phase, the ovulatory phase, and the luteal phase. The follicular phase is characterised by low levels of oestrogen and progesterone and high levels of the follicular stimulating hormone [FSH]. The ovulatory phase is characterised by a peak concentration of oestrogen and the peak of luteinizing hormone [LH]. The luteal phase is characterised by high levels of progesterone and low levels of FSH, LH, and oestrogen [75]. It is claimed that the gender differences in pain sensitivity is due in part to the effect of gonadal hormones [74]. For example, from a clinical point of view, some researchers established that there is an increase in pain sensitivity at times of the lowest oestrogen or rapidly fluctuating oestrogen in normally menstruating women [67, 76]. Moreover, it has been found that many clinical pain conditions in females are found to vary with the menstrual cycle phases and throughout pregnancy, mainly, temporomandibular (TMD) [67], migraine [77], tension-type headache [78, 79], fibromyalgia [80], and irritable bowel syndrome [81].

There are a substantial number of experimental studies that have used noxious stimuli to examine pain sensitivity in females throughout the menstrual cycle. Previous studies have demonstrated that there is a variation in pain reaction in normally menstruating women according to their cycle phase. A lower pain threshold [*i.e.* higher pain sensitivity] during the premenstrual phase [5 days before bleeding] has been reported by Herren who used pressure pain stimuli [82] and Procacci *et al.* [1974], who used radiant heat stimulation [83]. In contrast, a higher threshold and tolerances in the premenstrual phase have been found by Aberger *et al.* [1983] who used the muscle ischaemia task [84]. It is revealed that that the highest level of pain sensitivity was one week following menstruation (days 1-7), and the lowest level of pain sensitivity was during ovulation (days 15-21)[85]. It is documented that the effect of variation in gonadal hormone levels across the menstrual cycle on female sensitivity to pain was small and had only a minor contribution to gender differences in pain [70]. The result of a meta-analysis of studies investigating the relationship between pain sensitivity and the menstrual cycle conducted by Riley *et al.* [1999] suggested less pain sensitivity for pressure induced pain, thermal heat stimulation, cold pressor tests or ischaemic muscle pain was demonstrated during the follicular phase (days 6-11) in healthy menstruating females [86]. The least pain sensitivity for electrical stimulation was demonstrated in the luteal phase (days 17-23) [69]. In contrast, pain thresholds elicited by cold pressor stimuli in females was found to be higher during the late ovulatory phase (days 20-24) [87].

On the other hand, some investigators have concluded that there are no differences in pain sensitivity responses throughout the menstrual cycle [88 - 90]. A review by Sherman and LeResche (2006) revealed that there was no evidence that gonadal hormone changes across the menstrual cycle affect responses to experimental pain [76]. It has been reported that although females were found to be more sensitive to a range of pain modalities than males, menstrual cycle stages did not explain these differences [91]. A study done by Bartley and Rhudy (2013) also found no effect of the menstrual cycle on experimental pain [92].

It is clear that more research is needed in this area and as most of the experiments relied mainly on women reporting their menstrual cycle phase it is advised that future experiments should involve a hormonal essays and correlate that with pain sensitivity response. Another confounding factor which is often ignored is the stress and anxiety of women

during different menstrual cycle phases.

#### **1.3.4.2. Psychosocial Mechanisms**

A growing body of literature agrees that pain is affected by psychological factors and this effect of psychological factors gives an explanation for a number of differences connected with pain [9].

It has been demonstrated that the differences between males and females in sensitivity to pain are affected by psychological factors like anxiety [9, 93]. Moreover, anxiety has been recognised to be associated with gender differences in pain responses [94] and might be more associated with pain in males [7]. Each pain stimulus technique causes different levels of unpleasantness, for example, it has been stated by Rainville and others that in contrast to heat and electrical shock stimuli, cold and ischemic techniques are more likely to be accompanied by a higher level of unpleasantness [95]. Furthermore, in comparison with other noxious stimulus, the perfect pain stimulus to study the influence of anxiety is thought to be heat pain, because of its lower level of unpleasantness [95]. It is noticeable that there is a strong association between chronic pain in men and anxiety [96]. Although post-surgical pain is more intense in women than men, men are more troubled by low and persistent levels of pain [97].

Gender role is another psychological factor that might affect the difference in pain sensitivity response. The term “gender role” has been used to refer to a socially accepted group of features sanctioned to each sex [98]. It has been argued that gender roles seem to have an influence on sex differences in pain sensitivity response [9, 98]. Although the strength of the influence of gender roles on the sensitivity to pain is still uncertain [99, 100]. When Otto and Dougher [1985] measured gender roles and investigated its relationship with pressure pain, a significant correlation between masculinity-femininity and pain threshold was observed for males, but not for female participants [101]. In a different study, Dixon *et al.* (2004) investigated the relationship between gender-related personality types and pain sensitivity; and concluded that there is a negative correlation between masculinity-femininity scores and cold pain tolerance [102].

Although pain is a worldwide health problem affecting all populations, the elderly and women were found to be over-represented [103]; the role of age and sex/gender is unclear due to the inconsistency in research findings. Methodological variations in study design may be one factor leading to inconsistent findings. In experimental pain studies, the type of stimulus induction method used may influence outcome. Therefore, there is a need to discuss the different methods of experimental pain techniques, which will hopefully provide the theoretical guidance for the specific method to be used.

#### **1.4. Future Research**

There is a need for further research using the latest advanced quantitative sensory testing protocols to measure the function of small nerve fibres that are involved in nociception and pain sensitivity across the human life span. Findings from these studies should feed into and inform evidence emerging from other types of studies (*e.g.* brain imaging technique and psychometrics) suggesting that pain in the older humans may have unique characteristics that affect how old patients respond to intervention. This basic science approach should also complement the acquisition of clinical data relevant to age from patients with pain as while age, sex and other clinical data are routinely recorded in patients' reports, it is seldom for nurses and clinicians to include detailed reporting of pain episodes and its treatment, therefore several databases of medical records lack essential information about descriptors, severity and frequency of pain in many clinical pain conditions. Information about responses to different pain treatments is also lacking. To better understand how pain changes course through the human life span it is essential to obtain such information. Future research, therefore, has to fill the gaps and longitudinal databases should be improved. Therefore, we suggest that a much better future research strategy to better understand the mechanism of age-related pain should include basic science experiments in a controlled environment and encourage an epidemiological approach aimed to cover different pain conditions through the life span.

#### **CONCLUSION**

In conclusion, the critical appraisal of the literature suggests that the results of the experimental and clinical studies regarding age differences to pain contain some contradictions. This is because pain in older people is complex [104] and their response to different stimuli and to treatment may vary and future standardised testing and research methodologies are needed. However, data from the clinical studies are more consistent than experimental data and seem to point towards the fact that chronic pain increases in the elderly. Findings from the experimental studies on the other hand were contradictory, with pain threshold increasing with age in some studies *e.g.* [35, 105] and decreasing with age in

others *e.g.* [15, 31]. We suggested that a combined research approach should include a full battery of quantitative sensory testing to examine the same body sites under the same settings of different age groups to better inform the literature.

Furthermore, regarding sex differences to pain, most studies were consistent in the direction that females seem to be more sensitive to experimentally induced pain and more exposed to some diseases in comparison with males.

In addition, the causes underlying these differences, as well as the interaction between age, sex, and pain, are still unclear. More importantly, most of the studies have investigated the age differences and the sex differences to pain separately. So, there is a need to further examine the interaction between age, sex, and pain.

#### **ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

Not applicable.

#### **HUMAN AND ANIMAL RIGHTS**

No Animals/Humans were used for studies that are base of this research.

#### **CONSENT FOR PUBLICATION**

Not applicable.

#### **CONFLICT OF INTEREST**

The authors have no conflict of interest relevant to this publication.

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