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Application of the Neuromatrix Pain Theory to Understand Sex and Gender Differences in Chronic Pain

Mona H. Mathna[1], Joy C. MacDermid[2]

[1]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Menoufia University, Egypt
[2]Department of Physical Therapy, University of Western Ontario, London, ON

Email address
monamathna@hotmail.com (M. H. Mathna)

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Abstract
Since chronic pain is a complex phenomenon, a conceptual model may be useful in understanding this complexity. One conceptual model commonly used to explain chronic pain is the neuromatrix pain theory, which aims to explain the integrative role of the brain in pain generation. While this model does not specifically identify aspects of sex and gender that might affect pain; it may lend itself to this application. The objective of this paper is to explore the influence of gender and sex in the context of the neuromatrix theory for better understanding of the widely reported gender/sex difference in chronic pain experience. Understanding the difference between the meaning of gender and sex is essential, because this can help identifying and organizing the role of both gender and sex as different inputs to the neuromatrix. Sex refers to the biologic condition of an individual as being female versus male, while gender refers to the social role with which an individual identifies. Gender can influence the cognitive and affective components of pain. So, gender can be considered as cognitive and/or affective inputs to the neuromatrix, which can modulate the pain neurosignature within the neuromatrix and consequently influences pain responses. However, sex hormones play a vital role in production of sex difference in pain response. Estrogen can influence pain processing before the level of the neuromatrix resulting in change in the sensory signaling input to the neuromatrix. It can also influence the different anatomical constitutes of the neuromatrix. Another contributing finding that can help explaining the sex difference and also the individual variations among women in pain response is the genetic expression of estrogen receptors within the neuromatrix. Eventually, it seems that there are multiple inter-related factors that may interact to modulate the pain neurosignature within the neuromatrix and produce the gender/sex difference in pain response. Considering these factors can guide pain management in women, and can also identify sex/gender as predictors of chronic pain that may become future treatment targets.

1. Introduction

Pain has an important role in maintaining human health and safety; it warns us to respond to and treat the cause of pain. Memories of earlier pain incite the recognition and avoidance of potentially serious situations in the future. [1] Pain is a major health problem. It has been found that twenty percent of adults around the world suffer from pain; half of them are diagnosed with chronic pain yearly. [2] Chronic pain disturbs the lives of millions of people all over the world, and usually increases the social burden. [3]

Therefore, pain management is considered a basic human right. [4] Chronic pain has been defined as persistent pain for more than three months. [5, 6] In comparison to acute pain, chronic pain is difficult to explain because its cause is indefinite; however, it is usually associated with stress. It has been suggested that chronic pain is a disease, and not a symptom. [1]

It has been found that some chronic pain disorders such as fibromyalgia, migraine, temporomandibular disorders, and irritable bowel syndrome are more prevalent in women than in men. [7, 8, 9, 10] However, there is lack of the obvious pathology of these conditions, which makes it unclear to understand to what extent physiological factors may underlie this sex-related difference. [11] Several mechanisms such as psychosocial factors and sex hormones have been suggested to explain sex/gender difference in pain experience. [12, 13] The pathogenesis of chronic pain is complex. Therefore, an applicable conceptual paradigm is needed to guide chronic pain management and stimulate research about chronic pain. One such paradigm, which is helpful and can resolve chronic pain complexity, is the neuromatrix theory. [14] The purpose of this article is to employ the difference in the meaning between gender and sex to the neuromatrix pain theory for better understanding of the widely reported gender/sex difference in chronic pain experience.

2. Overview of the Neuromatrix Pain Theory

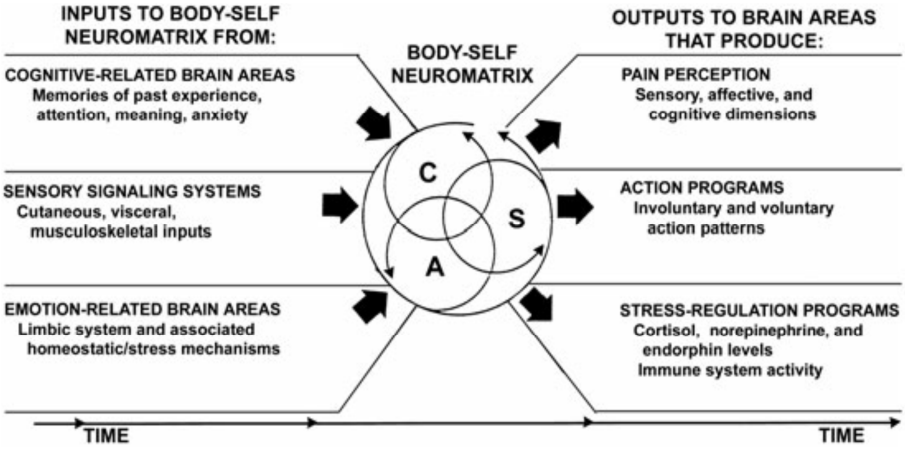

Figure 1. *The neuromatrix pain theory framework shows that the cognitive, sensory and affective neuromodules, which constitute the input portals to the neuromatrix, can contribute to the patterns of activity generated by the neuromatrix. The activity of the neuromatrix comprises the output patterns that produce multiple dimensions of pain experience as well as concurrent homeostatic and behavioral responses (Melzack, 2001). This framework is printed by permission from Dr. Ronald Melzack.*

The neuromatrix theory proposes that pain is a multidimensional experience produced by the neurosignature generated by the neuromatrix. The theory suggests that the neuromatrix is a large, widespread neural network in the brain, which extends between the thalamus and cerebral cortex, and then between the cerebral cortex and limbic system. The neurosignature is the characteristic pattern of neural activity generated by the neuromatrix. The neurosignature patterns may be stimulated by different types of sensory inputs. The theory also proposes that the neurosignature for the pain experience is determined by the neural construction of the neuromatrix, which is genetically predetermined. The inputs contributing to the neurosignature are cognitive, sensory, and emotional portals. The neurosignature is modulated by inputs from different parts of the body to produce a wide range of pain experiences. The neurosignature, which is a continuous outflow from the neuromatrix, bifurcates projecting two patterns. One pattern projects to the brain through the sentient neural hub where this pattern is converted into a continually changing stream of awareness and experience of movement, and another pattern projects to activate spinal cord neurons to produce muscle patterns for complex action. A third output of the neuromatrix is the stress regulation programs that are responsible for maintaining the homeostasis in the face of stress; if these regulatory programs fail to restore homeostasis, the neuromatrix may produce neural disturbance that can disrupt the neuromatrix activity pattern, and may also result in neural tissue destruction that gives rise to chronic pain. [15] So, the neuromatrix theory explains how chronic pain arises from abnormal reorganization in the neuromatrix. [16] Therefore, the neuromatrix theory to a great extent could explain the complexity of chronic pain pathogenesis. Before examining the ability of the neuromatrix theory to explain the sex/ gender difference in the pain, we should understand the difference between gender and sex. Terms sex and gender are not equivalent; sex refers to the biologic condition of an individual as being female versus male, while gender refers to the sex related social role with which an individual identifies. [12]

3. Gender and Neuromatrix

It has been noticed that some cognitive factors such as coping

and catastrophizing, and also affective factors such as anxiety and depression contribute to gender differences in pain. [17]

It has been found that women often suffer from more intense pain, and use more coping strategies such as social and emotional support than men. [18] Multiple studies have demonstrated that women score higher levels of pain coping and catastrophizing than men. [19, 20, 21] Also, it has been observed that among children and adolescents with chronic pain, girls often use pain catastrophizing and social support as a pain coping method, while boys often use behavioral distraction. [22] Several studies have found that the sociocultural and racial factors can interact with gender to modify the pain experience. [23, 17, 24] One cross-sectional study has found that there is significant association between social factors and presence of pain in women. [25] Interestingly, there is a strong association between female gender and some affective states as anxiety and depression. It has been shown that there is sex difference in anxiety, as women usually demonstrate higher levels of anxiety and are at higher risk to develop many anxiety disorders than men. [26] Also, it is widely reported that higher levels of anxiety is usually associated with increased both clinical pain and experimental pain sensitivity. [27, 18] Rollman (1995) has suggested that the increased level of anxiety in women is probably responsible for the sex differences in pain sensitivity. [28] It has been reported that there is a great association between depression and chronic pain, and also depression is more prevalent in women than men. [29] Marcus et al. (2008) in their study of sex differences in depression symptoms found that among persons with depression, women are more likely to suffer from chronic pain than men. [30] Therefore, gender can influence the cognitive and affective components of pain; and gender, by its definition (sex related social role), can be considered as cognitive and/or affective inputs to the neuromatrix, which can modulate pain neurosignature and consequently pain perception. The neuromatrix theory did not directly mention that social factors are possible inputs to the neuromatrix. However, it is understandable that social factors can influence both cognitive and/or affective domains. Moseley (2007), in his study "Reconceptualising Pain According to Modern Pain Science" considered social factors, work environment, cultural factors and beliefs as additional inputs to the neuromatrix that can modify the neurosignature and modulate pain perception. [31] Finally, we can consider that the neuromatrix theory has the ability to explain the gender difference in the pain.

4. Sex Hormones and Neuromatrix

4.1. Sex Hormones and Pain

Many of musculoskeletal pain conditions such as fibromyalgia syndrome (FMS), temporomandibular joint disorder (TMD), migraine, neck, shoulder, knee, and back pain are more prevalent in women. [32] Fibromyalgia syndrome affects more women than men and demonstrates the complexity of most chronic pain syndromes. [33] Melzack (2005) attributed the pain in women with FMS to estrogen, and proposed that estrogen stimulates the release of peripheral cytokines, which stimulates cortisol release; then, cortisol accumulates in tissues resulting in chronic pain. [1] If this is indeed the case, then this suggestion would mean that all women have fibromyalgia or chronic pain, but, this is not true. Fibromyalgia is estimated to affect only two to eight percent of the population, with a female -to-male incidence ratio between 7:1 and 9:1. [34, 35] So, we need to know, why do some women have fibromyalgia?

Experimental and clinical data point to the involvement of sex hormones in many chronic pain syndromes. It is found that changes in plasma estrogen levels are associated with frequent pain in women. [36] Furthermore, postmenopausal women who are using estrogen replacement therapy have an increased chance of developing chronic temporomandibular joint pain. [11] One study has analysed the menstrual cycle phases in healthy women and found that pain ratings were positively correlated with estradiol and progesterone during the luteal phase. Also, estradiol and progesterone increase across the menstrual cycle were positively correlated with pain increases. These findings denote that there is a relation between sex hormones pain response women. Interestingly, it has been observed that estrogen has a nociceptive effect in experimental animals. One experimental study has found that male rats injected intracerebroventricularly with estradiol for two days demonstrated higher levels of formalin-induced licking than rats injected with saline. [37] In contrast to estrogens, multiple studies have indicated that androgens have analgesic effects. [38, 39, 40, 41] It has been reported that there is an inverse relationship between plasma testosterone and work related neck and shoulder pain in female workers. [42] Another piece of evidence for the analgesic effect of androgens is the clinical finding that androgen levels are lower in both women and men with rheumatoid arthritis than in controls. [43] So, it seems that there is a relationship between sex hormones and chronic pain experience in women. However, how can sex hormones affect pain response? And what is the responsible for the individual variations in pain perception?

4.2. Role of Sex Hormones Before the Level of Neuromatrix

One experimental study has found that injection of glutamate, which is an endogenous analgesic substance, into the temporomandibular joint has stimulated the reflex activity of masseter muscle in both sexes; however, the muscle activity in females was more obvious than in males. [44] Interestingly, gonadectomy of these glutamate injected female rats abolished this sex difference and when these female rats were given estrogen replacement therapy, this sex difference reappeared. [45] Generally, stimulation of primary afferents results in release of glutamate, which can stimulate N-methyl-d-aspartate (NMDA) receptors, expressed on the second order neurons (in the dorsal horn of spinal cord) resulting in excitability of the second order neurons and

consequently pain. [46] In another experimental study adding NMDA to the cultured dorsal root ganglion neurons from both female and male animals resulted in significantly higher currents from the female neurons than from male neurons, and then when estrogen was added to both samples, the current from the female neurons was extremely higher than that from male neurons. [47] Also, it has been observed that antagonizing NMDA receptors can significantly enhance opioid analgesia in male more than female. [48] So, these findings denote that estrogen can induce nociceptive responses through its stimulant effect on NMDA receptor function at the level of spinal cord (before neuromatrix). Thus estrogen can influence pain processing before the level of the neuromatrix resulting in change in the sensory signaling input to the neuromatrix and consequently the sex difference in pain response.

4.3. Role of Sex Hormones at the Level of Neuromatrix

It has been found that estrogens can increase the excitability of hippocampus neurons, as it can increase the number of their dendrites' spines and also stimulate their excitatory synapses. [49] Moreover, estrogen can decrease Gamma-Aminobutyric Acid receptors inhibition in the hippocampus. [50] It has been observed that testosterone can also induce neural excitability but this effect has been attributed to its conversion to estradiol. [51] One experimental study has observed that male gonadectomy has markedly decreased the excitability of the hippocampus, while female gonadectomy did not reduce this excitability. [52] This finding may point to presence of sex difference in the structure of hippocampus, which is a part of the neuromatrix. Moreover, it has been has been shown that estrogen can excite neurons in the cerebral cortex, cerebellum and hippocampus by a non-genomic mechanism. [53] Experimentally, it has been found that genes encoding estrogen receptors (ERs) are widely expressed in many brain areas, mainly the hippocampus and hypothalamus. [54, 55] Moreover, it has been found that there are great numbers of the co-regulator proteins (either activators or repressors), which are responsible for modulation of the steroid receptors mediated transcription in the brain. These proteins demonstrate selective affinities to bind with ERs; this elective binding can determine the effects of ERs' ligands, and can also determine the interactions of ERs with other nuclear receptors, such as progesterone and androgen receptors. [56] So, the sex difference and also the individual variations among women in the pain response are probably due to the difference in the genetic expression of sex hormones' receptors within the neuromatrix. This coincides with the neuromatrix theory, which proposed that the neuromatrix is genetically determined. [1] Interestingly, it has been noticed that high levels of estradiol are associated with reduced sensitivity to different opioid agonists. [57] In one experiment, it has been found that men exhibited greater μ-opioid receptor binding in multiple brain regions, specifically the limbic system than women in response to the induced muscle pain. [58] This finding points to the possible interaction between sex hormones and the opioid receptors within the neuromatrix. Further, there is evidence that there are sex differences in the dopaminergic and serotonergic receptor function within the brain and estrogen can modulate the function of these receptors. [59]

So, it seems that there are multiple inter-related factors that may interact to modulate the pain neurosignature within the neuromatrix and produce such sex difference in pain. These factors include estrogen, which can affect different structures within the neuromatrix; genetic expression of estrogen receptors within the neuromatrix; possibility of sex difference in the structure of hippocampus; and the sex difference in the function of some neurotransmitters' receptors such as dopaminergic and serotonergic receptors within the neuromatrix.

5. The Relationship Between Gender, Sex and Stress

It has been noticed that some environmental factors such as chronic psychological distress can result in ovarian dysfunction with a significant decrease in the estrogen level. It has been shown that there is an interchangeable interaction between the hypothalamus–pituitary–adrenal (HPA) axis and hypothalamus– pituitary–gonadal axis, as both of them can influence each other. [60] Some findings can support the potential relationship between the HPA response to stress and estrogen. One of these findings is presence of the ERα in the cells of adrenal medulla of females. [61] Another finding is the fact that estrogen binding to the corticotropin releasing hormone (CRH) gene can increase the activity of CRH. [60] So, there is obvious link between sex, gender and stress. Interestingly, it has been noticed that symptoms of chronic pain disorders such as fibromyalgia syndrome are similar to that of corticosteroid withdrawal after long-term corticosteroid use. [62] This may denote that the biological cause of pain in chronic non-cancer pain disorders is cortisol dysfunction. One study has found that, patients with fibromyalgia syndrome have lower cortisol values than normal persons. [63] In contrast, another study has found that the cortisol level has been significantly higher in patients suffering from chronic non-cancer pain than in controls. [64] These studies demonstrate the empirical adequacy of the neuromatrix pain theory, which proposes that stress, as a threat input to the neuromatrix can induce cortisol dysfunction. Melzack (2005) suggested that chronic stress can stimulate cortisol increase which gets depleted by time and both cortisol increase (by accumulation in tissues) and depletion can induce in chronic pain. [1]

6. Clinical Implications

Integrating the neuromatrix pain theory into the clinical context is valuable. The neuromatrix theory draws up a theoretical model for pain, which can inform substantive

advances in the clinician's understanding of pain. Also, understanding the difference between gender and sex and applying this difference to the neuromatrix theory can guide pain management. For example, it can be used in pain physiology education approaches to explain to women with chronic pain that their physiology as a female can influence their pain and thus validate their experience; this may help them to cope with their pain and consequently improves the quality of their lives. Behavioural interventions may need to consider gender differences in pain inputs and intervention response; and drug interventions should consider sex-bsed differences.

7. Recommendations for Future Research

Hypothesis driven research to understand how gender and sex affect pain using the neuromatrix theory as a foundation, may identify gender and sex specific predictors of pain chronicity that may become future treatment targets. Predictors should include cognitive, sensory and emotional factors and test how they interact with each other within the neuromatrix to produce chronic pain; and how sex hormones can affect/modulate this interaction. Studies are needed to demonstrate how much sex hormones, gender traits, cultural, and social factors can predict pain chronicity, intensity and intervention response. These studies may lead to sex/gender-specific interventions that should be tested in clinical trials.

8. Conclusion

Unlike acute pain, chronic pain is difficult to explain because its cause is unclear. The neuromatrix pain theory can help explain the complexity of chronic pain but does not explicitly explain the widely reported gender/sex difference in chronic pain. Understanding the difference between the meaning of gender and sex is crucial, because this difference can help identifying and organizing the role of both gender and sex as different inputs to the neuromatrix. Both can modify the pain neurosignature within the neuromatrix and eventually modify the chronic pain experience. Gender relates to social roles, exposures and experiences that can be considered as cognitive and/or affective inputs to the neuromatrix. Sex, which is a biological status can also modify the pain neurosignature by different ways. Estrogen can influence pain processing before the level of the neuromatrix resulting in change in the sensory signaling input to the neuromatrix. Estrogen can affect stress regulation mechanisms and different anatomical constitutes of the neuromatrix. Moreover, the genetic expression of estrogen receptors within the limbic system, which constitutes a great part of the neuromatrix, plus the selective affinity of some co-regulator proteins to these estrogen receptors, may explain the sex difference and also the individual variations among women in pain response. So, realizing the difference between the meaning of gender and sex, and considering their impact on pain neurosignature can help identifying sex and gender as predictors of chronic pain that may become future treatment targets.

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