Central nervous system mechanisms of pain in fibromyalgia and other musculoskeletal disorders: behavioral and psychologic treatment approaches

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Pain is one of the most important and challenging consequences of musculoskeletal disorders. This article examines the role of central nervous system structures in the physiology of pain. It also describes the neuromatrix, a construct that provides a framework for understanding the interaction between physiologic mechanisms and psychosocial factors in the development and maintenance of chronic pain. This construct suggests that behavioral and psychologic interventions may alter the pain experience primarily through their effects on emotional states and cognitive processes. The literature on cognitive-behavioral interventions for patients with rheumatoid arthritis and osteoarthritis indicates that they are well-established treatments for these disorders. However, the efficacy of these interventions for patients with fibromyalgia has not been established. It is anticipated that the development of valid measures of readiness for behavioral change may allow investigators to identify the patients with musculoskeletal disorders who are most likely to benefit from cognitive-behavioral intervention. Curr Opin Rheumatol 2002, 14:45–51

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Abbreviations

ASMP	Arthritis Self-Management Program
CBT	cognitive-behavioral therapy
CNS	central nervous system
HPA	hypothalamic-pituitary-adrenal

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Patients and their physicians recognize pain as one of the most important and challenging consequences of musculoskeletal disorders [1]. However, the management of musculoskeletal pain is made difficult by incomplete understanding of the causes of the factors that determine patients' pain experiences. For many of these illnesses, such as rheumatoid arthritis and osteoarthritis, pain is clearly associated with nociceptive transmission arising from inflammation or degeneration of joints and soft tissue. In contrast, the widespread pain and tenderness that characterizes fibromyalgia is usually independent of tissue damage. Moreover, patients frequently display pain behaviors (verbal reports, daily activities) that are not consistent with the severity of tissue damage, although they are associated with psychosocial factors such as anxiety or depression. It is clear, then, that although musculoskeletal pain is influenced by rheumatologic disease activity and tissue damage, many other biological and psychosocial factors may contribute to the persistence of pain and patients' perceptions of the intensity and the sensory and affective qualities of their pain experiences.

Pain mechanisms and physiology

The perception of pain normally is initiated by a stimulus (*eg*, pressure, heat) that activates nociceptors in peripheral tissues. Primary nociceptive afferents ascend contralaterally and excite spinothalamic and spinoreticular neurons in the dorsal horn of the spinal cord through neurotransmitters such as glutamate, aspartate, substance P, and calcitonin gene-related peptide [2]. The electrical signals generated in these spinal neurons are then transmitted from the dorsal horn to the brain in three primary ascending tracts that project to the thalamus and the reticular formation. Stimulation of these brain structures excites neurons with connections to the primary and secondary somatosensory cortex, insular cortex, and other regions of the limbic forebrain, where the electrical signals are organized to form perceptions of the pain experience.

It is important to note, however, that central nervous system (CNS) structures may facilitate or inhibit nociceptive transmission at the dorsal horn level by modulating the release of neurotransmitters and the excitability of the pain transmission neurons [3]. Moreover, the function of these CNS structures may be influenced by

biologic processes such as infection or inflammation and by psychosocial factors such as emotional responses (*eg*, anxiety, depression), cognition (*eg*, belief in one's ability to manage pain), and environmental events (*eg*, acute threat, learned associations between environmental stimuli and pain) [4••].

Neuromatrix

Melzack [5] has proposed a model of the dynamic process of pain transmission and inhibition that also provides a framework for better understanding disorders, such as fibromyalgia, that are characterized by persistent pain in the absence of tissue damage. This model posits that the brain possesses a neural network comprised of pathways linking the thalamus, cortex, and limbic system, termed the body-self neuromatrix, that integrates multiple inputs to generate patterns of neural activity. This pattern-generating mechanism underlies awareness that one's body is distinct from the environment and perceptions of pain and pain behavior. The model also posits that the synaptic architecture of the neuromatrix is determined by genetic and sensory influences. Thus, the activity patterns produced by the neuromatrix are influenced by genetically-determined neural programs built into the neuromatrix and sensory and other types of inputs. Figure 1 shows that these inputs include (a) multiple sources of afferent input (*eg*, somatosensory, viscerosensory); (b) pathologic input (*eg*, from injured nerves); (c) endocrine, immune, and autonomic system activity; (d) medullary descending activity (*eg*, input from periaqueductal gray matter to the rostroventral medulla); (e) CNS plasticity (*eg*, enlargement of the peripheral receptive fields of spinal dorsal horn nociceptive neurons); (f) attention; and (g) psychosocial and health status factors (*eg*, cognition and emotional states). Therefore, any factor that alters the function of pain transmission or pain modulation pathways in the neuromatrix will influence pain perception and pain behavior. Moreover, disorders characterized by persistent pain may be maintained or influenced by alterations in the neuromatrix that cannot be restored to normal function.

Implications of the neuromatrix model for musculoskeletal disorders

The neuromatrix model provides a conceptual framework for understanding recent findings concerning the effects of psychosocial factors on pain in patients with musculoskeletal disorders. The model also provides a framework for the development and evaluation of the effects of behavioral and psychosocial interventions for pain management with these patients.

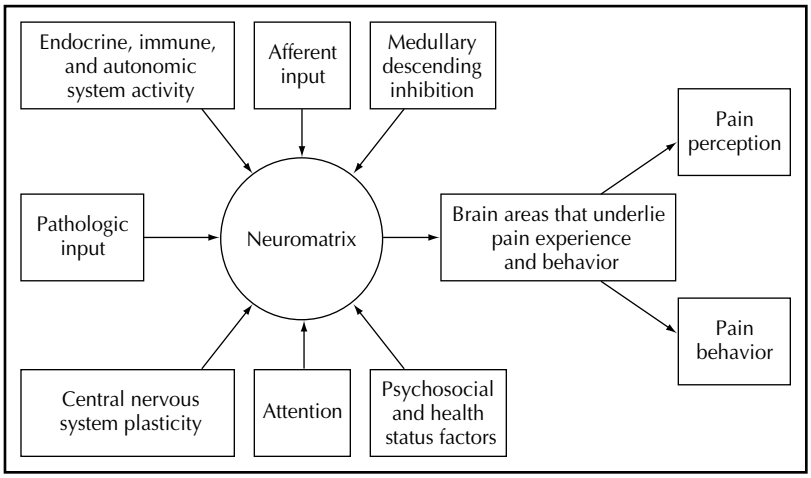
Psychosocial factors and pain

Depression, anxiety, and somatization

The neuromatrix model suggests that affective distress may enhance pain through several pathways, such as enhanced autonomic responses that increase limbic system activity [6] or reductions in serotonin or other neuropeptides involved in pain inhibition [7]. This distress also may influence pain behaviors such as health care utilization. Indeed, it is well established that depressive and anxiety disorders are common in patients with rheumatoid arthritis, osteoarthritis, and fibromyalgia, although they tend to occur most frequently in patients with fibromyalgia [8–9]. Consistent with the neuromatrix model, a history of major depressive episodes places patients with rheumatoid arthritis at risk for relatively high levels of pain and fatigue if the depressive episode is followed by persistent depressive symptoms [10–11]. However, the precise mechanisms underlying these relationships have not been elucidated.

Depression also is associated with a higher frequency of health care visits to physicians in patients with rheumatoid arthritis [12]. Similar observations have been made in patients with osteoarthritis and fibromyalgia. A 1-year

Figure 1. Model of the neuromatrix



The neuromatrix is a widespread network of brain neurons that generates patterns of activity responsible for perceptions of pain as well as reflexive and complex pain behaviors. Adapted with permission [5].

longitudinal study of Health Maintenance Organization patients with osteoarthritis found that low levels of well-being are significantly associated with relatively high health care utilization rates, even after controlling for age and previous health care system usage [13]. A recent cross-sectional investigation revealed that, after controlling for demographic variables, time since pain onset, and psychiatric morbidity, the variables that best differentiate patients with fibromyalgia from community residents with fibromyalgia who have not sought medical care are relatively high levels of depression, anxiety, and pain; high frequencies of recent stressful experiences; and low levels of self-efficacy [14].

Anxiety about behaviors or events that are likely to evoke increased pain intensifies the pain and other somatic experiences of patients with fibromyalgia [15]. There also is preliminary evidence that patients with high pain anxiety levels experience increased pain and exhibit increased functional brain activity in the right anterior cingulate cortex during exposure to sham stimulation [16]. However, a small number of promising case studies indicate that gradual exposure to activities or environment stimuli that evoke pain anxiety in people with chronic pain reduces their reports of pain [17].

Finally, somatization, or the tendency to experience a large number of medically unexplained symptoms, is a significant risk factor for the development of future chronic, widespread pain [18]. One interpretation of this finding is that persistent, widespread pain is a somatic manifestation of psychologic distress [18]. It should be noted, however, that women with the abnormal pain sensitivity and chronic widespread pain associated with fibromyalgia are significantly more likely than control subjects to show a functional polymorphism in the promoter region of the serotonin transporter gene (*5-HTT*) [19]. These women also are more likely than healthy persons to report a wide array of medically unexplained somatic symptoms. Thus, it may be that genetic influences on pain sensitivity mediate, in part, the relation between somatization and the development of widespread pain.

Stress and neuroimmune interactions

Musculoskeletal disorders produce numerous stressors that may influence patients' pain experiences and behavior. Among patients with rheumatoid arthritis, high levels of stress lead to increases in joint tenderness, global pain ratings, and altered immune system responses [20]. It also has been shown in healthy persons that stress is associated with increased production of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α [21•]. Conversely, stress reduction interventions consistently produce reductions in pain and joint count measures in patients with rheumatoid arthritis [22,23•]. These findings have contributed to the increasing interest in the role of neuroimmune interactions in the development and maintenance of persistent pain in musculoskeletal disorders [4••,24].

Recently, basic scientists have produced evidence that spinal cord glia (microglia and astrocytes) appear to contribute to exaggerated pain states through the release of a variety of neuroactive substances that enhance pain such as prostaglandins, excitatory amino acids (*eg*, glutamate, aspartate), nerve growth factors, and nitric oxide [25]. These findings have important potential implications for our understanding of inflammatory disorders such as rheumatoid arthritis. They also may lead to greater understanding of the persistent pain and abnormal pain sensitivity associated with fibromyalgia, given that persons with this disorder exhibit elevated cerebrospinal fluid levels of substance P, nerve growth factor, and metabolites of nitric oxide [26–30]. However, no studies to date have examined the potential role of spinal cord glia in rheumatoid arthritis, osteoarthritis, or fibromyalgia.

Nevertheless, it has been found that abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis are involved in the association between stress and disease activity in patients with rheumatoid arthritis [31]. It also has been shown that both stress and inflammatory processes activate the HPA axis and production of cortisol, prolactin, and sex hormones [31]. Cortisol is involved in the downregulation of immune system activity, prolactin has proinflammatory effects, and ovarian hormones tend to enhance pain sensitivity [32]. It is not surprising, then, that patients with rheumatoid arthritis have low circulating serum cortisol levels, display abnormal diurnal changes in these levels [33], and have elevated serum levels of prolactin [34].

Similar abnormalities in HPA axis function have been noted in patients with fibromyalgia [35]. There also is evidence that women with fibromyalgia are characterized by perimenstrual increases in their pain, especially among those with premenstrual dysphoria [36]. The authors have proposed that abnormal function of the HPA axis may be involved in the extreme pain sensitivity displayed by patients with fibromyalgia through its effects on nerve growth factor and on the function of brain limbic system structures involved in pain processing [37]. In addition, recent evidence indicates that patients with fibromyalgia show significantly greater increases in pain during exposure to laboratory stressors than patients with knee osteoarthritis [38]. However, the mechanisms underlying this finding have not been identified.

Dysregulation of CNS function may contribute to the pain associated with osteoarthritis. There is evidence that saline infusion of the tibialis anterior muscle pro-

duces hyperalgesia and referred pain in patients with osteoarthritis of the lower extremities [39••]. Consistent with this finding, preliminary evidence from the authors' laboratory indicates that patients with knee osteoarthritis show significantly lower pain thresholds in response to pressure stimulation of the knee than control subjects. During suprathreshold stimulation of the knee, the osteoarthritis patients do not differ from control subjects in their ratings of pain intensity. However, the patients report higher levels of pain unpleasantness and display significantly greater increases in functional brain activity in the anterior cingulate cortex than control subjects [40]. These findings suggest that pain in osteoarthritis may be heightened by alterations in the function of CNS structures involved in processing nociceptive transmission from muscle and other soft tissues of lower extremity joints.

Behavioral and psychosocial interventions for pain management

The neuromatrix model posits that behavioral and psychosocial interventions that alter emotional states, attention, and cognitive processes may substantially influence the pain experiences and behavior of persons with persistent pain. Most of the interventions currently used for patients with musculoskeletal disorders are considered cognitive-behavioral therapies (CBTs). Although there are variations among these CBT interventions, all include treatment components involving education, training in relaxation and other pain coping skills, rehearsal of these newly learned skills in patients' home and work environments, and relapse prevention (*ie*, strategies designed to help patients retain their coping skills and avoid increases in pain or other symptoms after treatment). All of these components are considered necessary to teach patients to reduce or better manage their pain experiences and distress and maintain improvement in functional ability.

Since the mid-1980s, a substantial number of CBT interventions for patients with persistent musculoskeletal pain have been evaluated using randomized, clinical trial methodology. Bradley and Alberts [41] used the American Psychological Association's criteria [42] for empirically validated treatments to evaluate this literature in 1999 (Table 1). This review noted that CBT interventions and the Arthritis Self-Management Program (ASMP) [43] met criteria for well-established treatments for both rheumatoid arthritis and osteoarthritis. However, there were no well-established treatment interventions for patients with fibromyalgia. Based on the available empirical studies, CBT qualified only as an experimental therapy for patients with this disorder.

Rheumatoid arthritis

In rheumatoid arthritis, CBT interventions, compared with attention-placebo, consistently produce significant reductions in patients' pain ratings or displays of pain behavior, and they generally produce significant reductions in joint counts [22,44]. In addition, these interventions frequently produce improvements in patients' beliefs in their abilities to manage their symptoms, and reductions in medical service costs that persist for at least 12 to 15 months after treatment [45,46].

It is important to note that all of the CBT interventions described above have been studied using patient samples with well-established histories of rheumatoid arthritis. Recently, however, Sharpe *et al.* [23] proposed that early intervention with behavioral or psychologic

Table 1. American Psychological Association criteria for empirically validated treatments

Efficacy classification	Criteria
Well-established treatment	EITHER (1) At least two methodologically sound, randomized, controlled, clinical trials demonstrate (a) statistical superiority to appropriate placebo or another treatment or (b) equivalence to an already established treatment OR (2) A large series of methodologically sound, single-case design studies demonstrates superiority to appropriate placebo or another treatment AND (1) Studies use standardized treatment protocols (2) Characteristics of the patient sample are clearly specified (3) Studies demonstrating efficacy are conducted by two different investigators
Probably efficacious treatment	EITHER (1) Two studies show statistical superiority to a waiting-list control group OR (2) One methodologically sound, randomized, controlled clinical trial demonstrates (a) statistical superiority to appropriate placebo or another treatment or (b) equivalence to an already established treatment OR (3) A small series of methodologically sound, single-case design studies demonstrates superiority to appropriate placebo or another treatment
Experimental treatment	All interventions that do not meet criteria for well-established or probably efficacious treatments

Data from Chambless *et al.* [42].

treatments might produce greater benefit for these patients. These investigators examined the effects of adding an eight-session CBT intervention to standard medical care in patients who had been diagnosed with rheumatoid arthritis for an average of 12.6 months. Sharpe *et al.* [23] found that the patients who received CBT as an adjunct treatment did not differ in pain reduction from those who received only standard medical care. This finding suggests that effective medical intervention masked any potential effects CBT might have had on pain. More importantly, however, the patients treated with CBT reported significantly lower levels of depression at posttreatment and at 6-month follow-up than the patients receiving standard care. In addition, at 6-month follow-up, the CBT patients were characterized by significantly lower joint counts than those who received only standard care. Given the evidence that persistent depression predicts higher subsequent levels of pain [10,11], it is most important to determine whether early CBT intervention in addition to medical treatment might be superior to medical care alone in producing reductions in joint counts or in patients' pain ratings sustained for several years after diagnosis with rheumatoid arthritis.

Several recent studies have examined whether administering single components of CBT might produce patient improvements similar to those documented for complete intervention programs. These studies revealed that use solely of relaxation training [47] or coping skills training [48] produces no sustained improvements in pain, quality of life measures, or coping skill usage. It appears that the components of CBT intervention are most effective when delivered as part of a comprehensive package that includes relapse prevention.

Bradley and Alberts [41] described an interesting experimental therapy for patients with rheumatoid arthritis that involved privately describing stressful life events on home audio recordings over a 4-day period [49]. It was found that, at 3-month follow-up, patients who recorded their stressful life events reported significantly greater improvements in psychologic distress and functional ability than patients who recorded benign events for a period of 4 days. A recent study of rheumatoid arthritis patients compared the effects of privately writing about highly stressful life experiences for 20 minutes on three consecutive days with writing about plans for the upcoming day [50]. Patients who wrote about stressful experiences had significantly lower physician ratings of disease activity at a 4-month follow-up than control patients. However, further analysis of the data did not produce evidence that this outcome was mediated by changes in affect, social relations, stress, substance usage (*eg*, tobacco, alcohol), medications, or sleep [51]. At present, the recording of stressful life events must be considered an experimental therapy given that (a) it is not known whether experimental and control patients in these studies have similar beliefs regarding the potential efficacy of their recording exercises, and (b) different outcome measures have been used in the two published studies.

Osteoarthritis

In osteoarthritis, it has been shown that CBT intervention, compared with attention-placebo, produces significant reductions in patients' ratings of pain and psychologic disability that are maintained for at least 6 months posttreatment. In addition, CBT produces significant improvements in patients' ratings of physical disability from posttreatment to 6-month follow-up [52–54].

The ASMP is a standardized intervention designed to enhance patients' beliefs in their abilities to manage their pain, disability, and other arthritis symptoms. Numerous studies have documented the efficacy of the ASMP among patients with osteoarthritis and rheumatoid arthritis [43]. Although the effects of the ASMP have never been evaluated against those produced by attention-placebo, it has been found that this intervention produces significant reductions in patients' pain ratings and in arthritis-related physician visits that persist as long as 4 years after treatment [43]. Thus, the authors consider the ASMP a well-established treatment for patients with osteoarthritis and rheumatoid arthritis.

Recent studies have shown that it is possible to adapt the ASMP to produce significant improvements in health status among patients with heart disease, lung disease, and stroke similar to those found in patients with arthritis [55]. In addition, a Spanish language version of the ASMP produced improvements in health status and health care system utilization among Hispanic patients with osteoarthritis and rheumatoid arthritis that are consistent with those produced by the English language version of the intervention [56]. However, similar to the findings on the efficacy of CBT, it is not possible to reduce the number of sessions that comprise the ASMP without substantially reducing treatment efficacy [57]. It also has been reported that arthritis patients in the United Kingdom participating in the ASMP consistently vary from their counterparts in the United States in their responses to the Center for Epidemiologic Studies—Depression Scale [58]. This finding suggests that cultural variations, even among English-speaking populations, may adversely affect the validity of comparisons of the efficacy of the ASMP among different nations.

Fibromyalgia

Many investigators have examined the effects of CBT and other behavioral interventions on pain in patients with fibromyalgia [41]. However, few examinations of these protocols have included adequate experimental controls for the effects of special attention to participants in treatment trials or adequate follow-up evaluation. Al-

though several uncontrolled trials have suggested that coping skills training for patients with fibromyalgia may produce improvements in pain and function, none of the three attention-placebo–controlled trials performed to date have shown that psychosocial interventions are superior to placebo [59–61]. Thus, little progress has been made in the development and evaluation of CBT and other behavioral interventions for fibromyalgia since the authors' 1999 review [41]. Nezu *et al.* [62] recently reached a similar conclusion. These interventions must be considered experimental therapies.

Investigators who wish to perform well-controlled evaluations of the effects of CBT on pain in patients with fibromyalgia should consider that the efficacy of these interventions may be limited by several factors. All these factors appear to be more prominent in patients with fibromyalgia than in those with rheumatoid arthritis and osteoarthritis. They include the following: (a) the high frequency of psychiatric disorders in patients with fibromyalgia may reduce concentration or motivation to adopt and practice pain management skills; (b) CNS plasticity associated with fibromyalgia may limit the extent to which pain management skills alter the functioning of the neuromatrix; and (c) patients with fibromyalgia may develop pessimistic expectations concerning the potential efficacy of CBT interventions because of the poor outcomes they experience with most pharmacologic therapies; thus, they may be reluctant to become actively involved in treatment.

A recent positive development is the use of standardized instruments to classify patients with rheumatoid arthritis, osteoarthritis, and fibromyalgia [63–64]. Independent studies have attempted to classify patients with rheumatoid arthritis, osteoarthritis, and fibromyalgia into five stages of readiness for behavioral change [65]. The authors believe that further refinement and use of these instruments may contribute to understanding of the differences in outcomes found among the three patient groups. Moreover, it may be possible in the future to identify reliably the patients within each group who are most likely to respond positively to CBT or other behavioral interventions.

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