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## REVIEW

## Central Pain Mechanisms in the Rheumatic Diseases

### Future Directions

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#### Introduction

Pain is a prominent component of many rheumatologic conditions and is the result of a complex physiologic interaction of central and peripheral nervous system signaling that results in a highly individualized symptom complex. Pain is frequently categorized as acute or chronic (generally >3 months' duration). Chronic pain is not simply acute pain that has lasted longer; it is more likely to be influenced by input from the central nervous system, whereas acute pain is often attributable primarily to inflammation and/or damage in peripheral structures (i.e., nociceptive input).

The prominent role of central factors in chronic pain is highlighted by the fact that there is currently no chronic pain condition in which the degree of tissue inflammation or damage alone (e.g., as measured by radiographs, magnetic resonance imaging [MRI], or endoscopy) accurately predicts the presence or the severity of pain. Central factors alter pain processing by setting the “gain,” such that when peripheral input is present, it is processed against a background of central factors that can enhance or diminish the experience of pain. There are very large interindividual differences in

these central nervous system factors that influence pain perception, such that some individuals with significant peripheral nociceptive input (e.g., from joint damage or inflammation) will feel little or no pain, whereas others are very pain sensitive, and they can experience pain with minimal or no identifiable abnormal peripheral nociceptive input. This emerging knowledge has important implications for pain management in individuals with chronic rheumatologic disorders.

#### Pain in rheumatologic disorders

Although most patients seen by rheumatologists have pain as their presenting complaint, most rheumatologists have little formal training about contemporary theories regarding pain processing or pain management. Because of this, educating rheumatologists and others involved in the care of individuals with musculoskeletal pain has become a priority. The American College of Rheumatology Pain Management Task Force highlighted this in an initiative to increase awareness and call for organized research and education concerning chronic pain (1). Chronic pain may encompass pathology of the joint, skin, muscles, or peripheral nerves associated with rheumatologic diseases. A better understanding of chronic pain mechanisms will help us understand individual differences in pain among patients with rheumatic diseases, and this will in turn allow for a more targeted approach to treatment (i.e., personalized analgesia) (2).

#### The concept of centralized pain

The term “central pain” was originally used to describe the condition in individuals who developed pain

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following a stroke or spinal cord lesion. In this case, “central” refers to the fact that the lesion leading to pain occurred within the central nervous system (CNS). More recently, however, the term has been expanded to describe any CNS dysfunction or pathologic condition that may be contributing to the development or maintenance of chronic pain (3), which includes, but is not limited to, important contributions from psychosocial aspects of pain perception. Another term that has often been used to describe this same phenomenon is “central sensitization.” The term central sensitization was originally used to describe a state in which the spinal cord amplifies afferent signals out of proportion to peripheral tissue changes. This term has the same problem as the term “central pain” because it originally referred to a specific mechanism, representing only one potential cause of augmented CNS pain processing (4).

For clarity, we will use terms such as central augmentation or amplification to refer more broadly to central mechanisms that enhance the perception or modulation of pain differentially between individuals. We will use the term centralization of pain to refer to a common process that seems to occur to a vulnerable subset of individuals with any chronic pain state, wherein pain primarily due to peripheral nociceptive input is subsequently amplified by central factors, such that both peripheral and central factors are then contributing to the individual’s perception of pain. This latter phenomenon is particularly important for rheumatologists to identify because these are individuals in whom our commonly used peripherally directed therapies (e.g., disease-modifying antirheumatic drugs [DMARDs], surgery) are unlikely to be effective as sole therapies.

Centralized pain was originally thought to be confined to individuals with rare structural causes of pain or those with idiopathic or functional pain syndromes, such as fibromyalgia (FM), headache, irritable bowel syndrome (IBS), temporomandibular joint disorder (TMJD), and interstitial cystitis (5). These pain syndromes have been shown to be very familial/genetic (e.g., the risk of developing FM is 8-fold higher in first-degree relatives of patients with FM) and to coaggregate in families (3,6). Twin studies also support a strong familial basis for pain as well as for this cluster of coaggregating symptoms (7,8). Even if these individuals are initially thought to have new onset of a regional pain syndrome, closer questioning often reveals that they have had many different regions of chronic pain over the course of their lifetime or even at present (9). Thus, taking both a personal history of chronic pain and a family history of chronic pain is a clinical pearl that can

be helpful in identifying individuals who have (or are at risk of developing) prominent centralization of pain.

Another marker of “central” pain is the occurrence of multifocal pain in conjunction with other centrally mediated symptoms, such as fatigue, insomnia, memory difficulties, and mood disturbances (10,11). One of the simplest ways to identify individuals whose pain has become centralized is to suspect that this has occurred when those with chronic pain have several of these other symptoms as comorbidities (3,12). Regarding the clustering of co-occurring somatic symptoms, as well as the higher than expected rates of mood disorders, the leading pathophysiologic theory concerning these central pain states is that centrally acting neurotransmitters that are known to be abnormal and likely to play a role in causing the pain in these conditions (e.g., low norepinephrine, GABA, or serotonin levels and high glutamate or substance P levels) also play prominent roles in controlling sleep, mood, alertness, etc. (3,13). This hypothesis is best supported by the fact that when centrally acting analgesics, such as selective serotonin and norepinephrine reuptake inhibitors (SSNRIs), gabapentinoids, tricyclics, or  $\gamma$ -hydroxybutyrate, are effective in a given patient with chronic pain, these drugs typically lead to improvements in one or more of these other symptom domains besides pain (14–16).

In addition to the study of symptom domains in central pain states, significant advances have been made in our understanding of the pathogenesis of chronic pain. The hallmark biologic finding common to these “centrally driven” conditions is that most individuals have a diffuse CNS hyperalgesic state that is identifiable by quantitative sensory testing and can be corroborated by functional neuroimaging (6,17–19). Data from quantitative sensory testing and functional neuroimaging studies suggest wide individual variations in pain and sensory sensitivity that adhere to a bell-shaped distribution across a wide variety of chronic pain states, with a subset of individuals displaying hyperalgesia or augmented CNS activity across pain states (3,6,18,20,21). Some of the discrete conditions originally identified as being central pain states because of the presence of diffuse hyperalgesia and a lack of obvious, ongoing peripheral nociceptive input include FM, IBS, TMJD, tension headache, interstitial cystitis, and vulvodinia (22–29).

The baseline presence of hyperalgesia and/or the absence of descending analgesic activity has not only been shown to be present in individuals with these centralized pain states, but has also been shown to be an important risk factor for a number of adverse pain

outcomes, including predicting the subsequent intensity of an acute painful experience, the analgesic requirements following surgery, and the subsequent development of chronic pain (30–32). This latter phenomenon was first demonstrated in a study by Diatchenko and colleagues (33), who performed a longitudinal study of 202 young, pain-free women whose cases they followed for 2 years, with the outcome of interest being the development of new-onset TMJD. An individual's pain threshold at baseline (i.e., while asymptomatic) was a strong predictor of the development of TMJD, since any individual on the "hyperalgesic side" of a bell-shaped curve of pain sensitivity at baseline was found to be nearly 3 times as likely to develop TMJD as an individual in the bottom half of pain sensitivity.

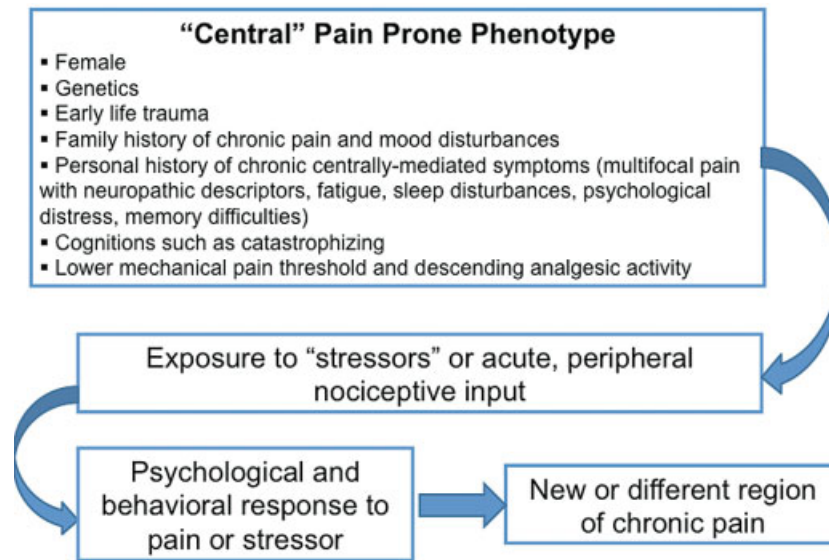
This study was among the first to highlight the strong role that certain genes play in turning up the "gain" on pain processing (6,33,34) and in identifying one cause of a "chronic pain-prone phenotype." Hypersensitivity of nonpainful stimuli in sensitized pain patients is a hallmark of chronic pain. The early genetic data were consistent with those of studies performed by Zubieta et al (35), who several years earlier, had shown that catechol-*O*-methyltransferase (COMT) polymorphisms predicted pain thresholds (as measured both by quantitative sensory testing and by functional neuroimaging) in healthy individuals. The same COMT gene risk allele has subsequently been shown to be more common in conditions such as FM and to exert a relatively large effect in experimental pain sensitivity in humans, as well as responsiveness to and side effects from commonly used analgesics (35–39). Just as we know of tremendous variability in pain sensitivity between strains of rodents, there similarly is great variability in pain sensitivity in humans (40). At least 5 sets of genes are associated with an individual's pain sensitivity and increase their likelihood of developing one or more chronic pain states. These include COMT (an estrogen-sensitive enzyme that may play a more prominent role in females), GTP cyclohydroxylase, types 2 and 3 adrenergic receptors, a P2X<sub>7</sub> receptor pore, and sodium or potassium channel genes (35,41–46). While some genes have been consistently shown to confer a higher risk of pain sensitivity or the development of chronic pain, this is a rapidly evolving area, and not all studies have demonstrated the same associations (41,47–49).

Kato and colleagues (8), using a large Swedish twin registry, performed a series of studies that first showed the comorbidities with chronic widespread pain, and then later, they examined a number of these central

or "functional" pain syndromes and the relationship of these symptoms to those of depression and anxiety. Those studies clearly demonstrated that functional somatic syndromes, such as FM, CFS, IBS, and headache, have latent traits (e.g., multifocal pain, fatigue, memory and sleep difficulties) that are different from, but overlap somewhat with, psychiatric conditions such as anxiety and depression. These findings are also consistent with the results of functional neuroimaging studies. For example, individuals with FM alone primarily have increased activity in the regions of the brain that code for the sensory intensity of stimuli (e.g., the primary and secondary somatosensory cortices, posterior insula, thalamus), whereas the FM patients with comorbid depression also have increased activation in brain regions coding for the affective processing of pain, such as the amygdala and anterior insula (50). The notion that there are 2 overlapping sets of traits, one being pain and sensory amplification and the other being mood and affect, is also supported by genetic studies of idiopathic pain syndromes (6). Twin studies have also been useful in helping tease out potential underlying mechanisms versus "epiphenomena." Those investigators suggested that there is evidence of a problem with biologic sensory amplification in the affected twins (51).

As with most illnesses that may have a familial or genetic underpinning, environmental factors may play a prominent role in triggering the development of FM and other centralized pain states. Environmental "stressors" temporally associated with the development of widespread pain include early life trauma, physical trauma (especially involving the trunk), and certain infections, such as hepatitis C virus, Epstein-Barr virus, parvovirus, Lyme disease, and emotional stress. The disorder is also associated with other regional pain conditions or autoimmune disorders (52–54). Of note, each of these "stressors" only triggers the development of fibromyalgia and/or chronic fatigue syndrome in ~5–10% of individuals who are exposed; the overwhelming majority of individuals who experience these same infections or other stressful events regain their baseline state of health.

In fact, emerging evidence from a number of different areas in the study of pain suggests that the same characteristics that are often attributable to FM patients in fact more broadly represents a "pain-prone phenotype." As shown in Figure 1, female sex, early life trauma, a personal or family history of chronic pain, a personal history of other centrally mediated symptoms (insomnia, fatigue, memory problems, mood disturbances), and cognitions such as catastrophizing have all been shown to be present in subsets of individuals with



**Figure 1.** Development of expanded pain regions in patients prone to experiencing central pain.

any chronic pain state and to predict which individuals are more likely to transition from acute pain to chronic pain.

Functional neuroimaging studies, especially those using functional MRI, also corroborate the findings of quantitative sensory testing for diffuse hyperalgesia/pain augmentation by demonstrating that individuals with central pain states have increased neuronal activity in pain-processing regions of the brain when they are exposed to stimuli that healthy individuals find innocuous (29,55–57). Several meta-analyses of functional MRI studies have summarized the brain regions that show activation when experimental pain is applied to human subjects, and these generally are consistent with the findings of single-photon-emission computed tomography (SPECT) and positron emission tomography (PET) studies noted above. The main components of this pain-processing matrix are the primary and secondary somatosensory cortex, the insular cortex, the anterior and midcingulate cortex, the posterior cingulate gyrus, and the thalamus; that is, the pain system involves somatosensory, limbic, and associative brain structures (58,59). Within a single brain region, such as the insula, the posterior insula is more involved in sensory processing and the anterior more involved in affective processing, and even the left-to-right balance of insular activity may be associated with the emotional valence of pain (60).

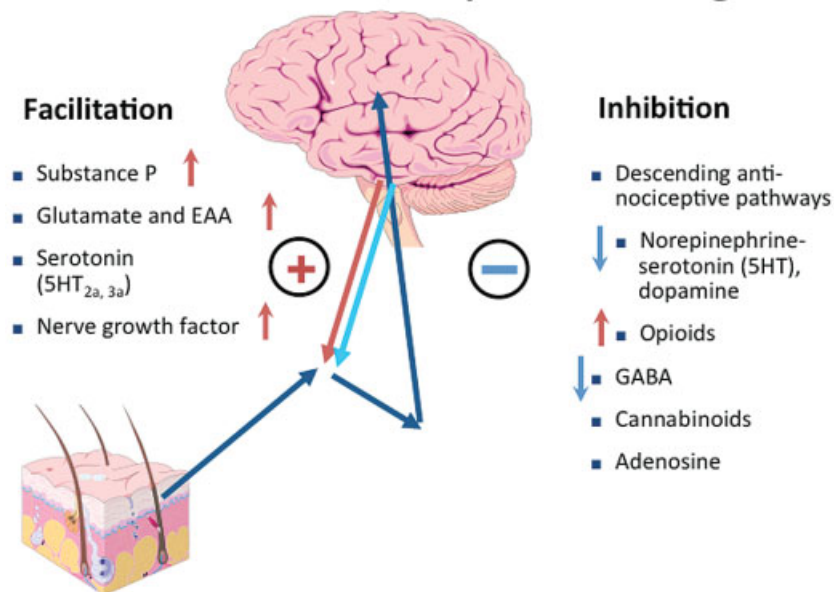
Many potential mechanisms can cause augmented central pain processing. The two receiving the

most attention and study have been increased wind-up and diminished descending analgesia or conditioned pain modulation. Wind-up is a perceived increase in pain intensity when a stimulus is repeated above a certain rate and is mediated by C fibers. Descending analgesia is a function of descending neural pathways that form a pain-modulating circuit. The integrity and magnitude of this conditioned pain modulation (CPM), or diffuse noxious inhibitory control (DNIC), system can be tested by using 2 separate painful stimuli and observing the fact that experiencing the first painful stimulus can reduce the perceived intensity of the second one. While both wind-up and CPM can be tested experimentally, data thus far suggest that the study of descending endogenous analgesic pathways holds the most promise for successfully identifying those with central predominance to their pain. For example, attenuated descending analgesic activity (experimentally observed as reduced DNIC or CPM) is seen in 10–20% of controls, but this deficit is demonstrated in ~60–80% of individuals with conditions such as FM or IBS (61–66). Neither diffuse hyperalgesia nor reduced DNIC/CPM (deficiencies in descending analgesic activity) is generally seen in individuals with psychiatric disorders such as depression (50,67).

An analogy of an increased “volume control” or “gain” setting on pain and sensory processing is supported by studies from a variety of sources. Elevated levels of neurotransmitters that tend to be pronocicep-



## CNS Influences on Pain and Sensory Processing



**Figure 2.** Influences of the central nervous system (CNS) on pain and sensory processing. Recent studies have demonstrated that an individual's "set point" or "volume control setting" for pain is determined by a variety of factors, including the levels of neurotransmitters shown on the left, which facilitate pain transmission (turn up the gain or the volume control), or the neurotransmitters shown on the right, which reduce pain transmission. Thus, high levels of the neurotransmitters on the left or low levels of those on the right would be capable of causing the diffuse hyperalgesia (increased volume control) that is seen in a variety of chronic pain states. EAA = excitatory amino acid; 5-HT<sub>2A</sub> = 5-hydroxytryptamine H<sub>2A</sub>; GABA =  $\gamma$ -aminobutyric acid.

tive (those shown on the left side of Figure 2) or reduced levels of neurotransmitters that inhibit pain transmission (those shown on the right side of Figure 2) have a tendency to increase the volume control, and drugs that block the neurotransmitters shown on the left Figure 2 or augment the activity of those shown on the right will typically be found to be effective treatments, at least for a subset of individuals with this spectrum of illness. As noted, there is evidence of increases in the CSF levels of substance P, glutamate, nerve growth factor, and brain-derived neurotrophic factor, and low levels of the metabolites of serotonin, norepinephrine, dopamine, and GABA can lead to an "increase in the volume control" and augmented pain and sensory processing (68–72). The only neurotransmitter system that has thus far been studied and not found to be inconsistent in a direction that would cause augmented pain transmission is the endogenous opioid system. This may be one reason why opioid drugs do not work well in the treatment of FM and related centralized pain conditions (73,74).

### Potential role of peripheral factors in central pain states

Immunologic cascades play a role in the maintenance of central sensitivity and chronic pain, which is enhanced through the release of proinflammatory cytokines by CNS glial cells; thus, the traditional paradigm regarding inflammatory versus noninflammatory pain may gradually become less dichotomous. As may be expected in any complex biologic system, a delicate apparatus of checks and balances is at work in the spinal transmission of pain. Furthermore, studies suggest that maintenance of central augmentation requires persistent noxious peripheral input, even in syndromes such as IBS and FM, which are characterized by the absence of well-defined, localized, pain-causing lesions (75). In fact, a recent study of 68 fibromyalgia patients with myofascial pain syndromes and 56 fibromyalgia patients with regional joint pain showed that peripheral trigger point injections and hydroelectrophoresis ameliorate fibromyalgia pain and increase pain thresholds at sites distant

from the therapeutic interventions, providing further evidence that painful peripheral stimuli contribute to the perpetuation of central augmentation interventions (76).

### The role of centralized pain in classic rheumatic diseases

Rheumatologists have known for some time that as many as 15–30% of individuals with classic autoimmune or rheumatic disorders also have comorbid FM, which was once referred to as “secondary FM” (77). These rates are much higher than the prevalence of FM in the general population (2%), suggesting that pain and/or stress accompanying chronic rheumatic diseases is one way that conditions such as FM can be triggered. Triggering of a centralized pain state can also be seen with certain types of trauma, such as motor vehicle collisions, by infections such as *Borrelia burgdorferi* in Lyme disease or Epstein-Barr virus, and following surgery or deployment in war (78–81). This suggests that many biologic stressors, especially those accompanied by acute pain, are capable of triggering centralization or chronic pain.

Wolfe coined the term “fibromyalginess” to connote the fact that regardless of whether individuals with rheumatic disorders have FM as a “categorical” diagnosis (i.e., yes or no) or whether this construct is measured as a continuous variable, the more general construct of FM is highly associated with levels of pain and disability across all rheumatic disorders (82,83). Fibromyalgia (dichotomous diagnosis) and fibromyalginess (measured as a continuous variable) directly affect traditional measures of disease activity and severity, and have implications for clinical practice (84). Partial fulfillment of the 2010 revised criteria for FM may prove useful in discerning patients who are at risk of developing chronic pain but do not meet diagnostic criteria for FM. The degree of fibromyalginess also influences objective and subjective responses to therapy with biologic and non-biologic DMARDs in RA and predicts worse pain and functional status following total joint arthroplasty and back surgery.

**Osteoarthritis (OA).** Historically, the “disease” of OA has been viewed primarily as damage to the cartilage and bone. As such, the magnitude of damage or inflammation of these structures should predict symptoms. Population-based studies suggest otherwise; 30–50% of individuals with moderate-to-severe radiographic changes of OA are asymptomatic, and ~10% of individuals with moderate-to-severe knee pain have normal findings on radiography (85,86). Psychological fac-

tors do account for some of this variance in pain and other symptoms, but only to a small degree (87,88). The fact that central factors may play a pivotal role in OA helps to explain the fact that comorbid somatic symptoms known to be associated with central pain conditions (e.g., fatigue, sleep problems) are very common in OA and are not explained by a purely “peripheral” model of this disorder (89–91).

Moreover, for some time, there have been small studies suggesting that OA patients display diffuse hyperalgesia to mechanical or heat stimuli (92). Kosek and Ordeberg (93) demonstrated that individuals with OA of the hip had reduced descending analgesic activity, which partially normalized following hip arthroplasty, suggesting that the central factors were being at least partly driven by peripheral nociceptive input. Since then, larger and more comprehensive studies have been performed, showing that groups of individuals with OA have lower overall thresholds for pain than do controls and have less efficient descending analgesic activity (92,94). Most recently, Gwilym and colleagues (20,95) used both experimental pain testing and more sophisticated functional neuroimaging procedures to show evidence of augmented CNS processing of pain in 20 OA patients and then showed in a separate study that atrophy of the thalamus was seen at baseline in OA and improved following arthroplasty. Finally, recent randomized controlled trials have demonstrated that compounds that alter pain neurotransmitters centrally, such as serotonin and norepinephrine (e.g., duloxetine, tricyclics), are efficacious in OA (96,97).

This does not at all mean that peripheral factors are unimportant in OA. A recent study by Neogi and colleagues (98) elegantly demonstrated that in individuals with asymmetric knee OA, the pain levels in each knee strongly related to joint space narrowing in the affected knee. The aggregate data instead suggest that in some individuals, central factors are superimposed upon the more traditional peripheral factors (targeted by nonsteroidal antiinflammatory drugs [NSAIDs], for example) leading to the need for a broader and more flexible approach to diagnosis and treatment.

**Systemic lupus erythematosus (SLE).** For some time, it has been suspected that FM is a common comorbid condition in SLE and confounds both the diagnosis and treatment of SLE (99–101). For example, just as with other rheumatic disorders, neither the degree of inflammation nor the degree of damage is highly associated with pain, fatigue, function, or other symptoms of SLE (102–104). Instead, the presence or absence of comorbid FM (which occurs in ~20% of

patients with SLE as well as other autoimmune disorders) is often the largest predictor of pain, fatigue, and function in patients with SLE (77,105). FM and phenotypical features of centralized pain are more related to quality of life measures than to disease activity per se (106). As individual domains, the presence of FM in SLE is most closely associated with fatigue, sleep disturbances, psychiatric disturbances, and work disability (107–109).

Additional studies are needed to explore the role that the “centralization-prone phenotype” plays in predicting which SLE patients will eventually develop comorbid FM or centralization of their pain. There has been very little quantitative sensory testing performed to date in SLE. Hyperalgesia, as crudely measured by a tender point count, is an uncommon finding in groups of SLE patients and is related to measures of health status and disease activity (110). Only a single published study has used functional neuroimaging in SLE. Areas of CNS hypoperfusion noted in patients with SLE overlapped with those seen in patients with FM alone, as well as in patients with SLE and FM in combination (111).

**Rheumatoid arthritis (RA).** In contrast to FM and OA, RA is characterized by systemic inflammation. Although inflammation contributes to pain in RA, it may not be the only factor. For many patients, pain does not improve upon treatment with antiinflammatory DMARDs (82). Although few studies have specifically examined the role of central pain-processing mechanisms in RA, studies using dolorimetry to assess pain thresholds suggest that these other pathways may in-

clude deficits in central pain processing. Early, small studies suggested that groups of RA patients displayed deficits in central pain processing, including impaired descending analgesic activity (112,113). Wolfe et al (82) showed that fibromyalgia is very prevalent in RA patients, and there is increased morbidity in patients who have both RA and FM as compared to those who have FM alone (114,115). It is important to remember that centralization of pain may also have an impact on traditional measures of disease activity, such as the Disease Activity Score in 28 joints. Lee and colleagues (116) recently showed that in RA, the relationships between inflammation, psychosocial factors, and peripheral and central pain processing are intricately entwined. In their study of 59 female patients with RA, they demonstrated that C-reactive protein levels were inversely associated with pain thresholds at joint, but not nonjoint, sites, consistent with peripheral sensitization (116). In that study, sleep disturbances were associated with pain thresholds at both joint and nonjoint sites, indicating that central mechanisms (i.e., central sensitization) likely underlie the link between overall pain sensitivity and sleep problems.

#### Future directions

Current and future studies in the rheumatic diseases can be leveraged to take advantage of both “primary” and “secondary” manifestations of FM and centralized pain, both to learn more about FM and to learn more about the pathogenesis and underpinnings

### Clinical Characteristics of Central Pain

- Pain in many different body regions
- Higher personal lifetime history of chronic pain
- Multiple somatic symptoms (e.g., fatigue, memory difficulties, sleep problems, mood disturbance)
- Sensory stimuli sensitivity (e.g., bright light, loud noises, odors, other sensations in internal organs enhanced)
- More common in women
- Strong family history of chronic pain
- Pain triggered or exacerbated by stressors
- Generally normal physical examination except for diffuse tenderness and nonspecific neurological signs

**Figure 3.** Characteristics of patients with rheumatologic diseases that may have contributions from central pain mechanisms.

of chronic pain more generally. Subsets of individuals in the population are more susceptible to developing chronic pain and somatic symptoms following exposure to sustained peripheral nociception and stress, and the clinical and biologic features of these susceptible individuals are reminiscent of those in patients with subclinical FM, which has been characterized as a “centralization-prone phenotype,” as outlined in Figure 3. When these individuals are exposed to the ongoing pain and stress associated with a chronic rheumatic disease, full-blown FM may be triggered in susceptible individuals. Patients with OA, RA, or SLE whose pain has already become “centralized” may show higher levels of pain intensity and disease activity for the same degree of inflammation or structural damage and may be less responsive to classic, peripherally directed pharmacologic (DMARDs) and nonpharmacologic (surgery) therapies (19,117).

There is significant support for this idea, especially given recent evidence of prominent CNS contributions to pain in conditions such as OA, RA, and low back pain (20,29,44,82,97,118). Across the rheumatic disorders, individuals with higher degrees of fibromyalgias may preferentially respond to “centrally acting” drugs (e.g. tricyclics, SSNRIs, gabapentinoids), whereas those without evidence of centralization of their pain will preferentially respond to drug classes historically believed to work better on peripheral/nociceptive pain (e.g., NSAIDs, opioids, DMARDs, surgery). Support for these hypotheses would tremendously advance our ability to offer personalized analgesia in routine clinical practice.

The overall direction of chronic pain research is a paradigm shift in the diagnosis and treatment of pain in individuals with rheumatic disorders. Instead of considering pain and other symptoms associated with OA, RA, and SLE to be primarily due to peripheral damage or inflammation (i.e., nociception), the appropriate “phenotyping” (recognition of patients with traits and states associated with the risk of developing chronic pain) of patients with chronic pain can identify subsets of individuals with these disorders that have prominent CNS contributions to their symptoms. Individuals with these diseases will likely respond differentially to DMARDs and nondrug therapies (such as surgical procedures performed for pain). Since arthroplasty and other surgical procedures performed to relieve chronic pain are very expensive procedures and since it is acknowledged that 20–40% of individuals receiving such procedures continue to have significant knee pain at 1–2 years (119), a tremendous opportunity exists for developing para-

digms by which to identify good (or poor) candidates for these or other “analgesic surgeries,” rather than subjecting individuals to a procedure from which they would be unlikely to derive any benefit. The same holds true for many other procedures performed to treat pain, as well as for the use of biologic immunosuppressive agents in patients with persistent pain but equivocal evidence of ongoing inflammation.

While there is knowledge to be gained from prior studies in other centrally mediated syndromes, rheumatologists should lead the way in developing and field-testing new phenotyping or identification measures for patients with rheumatologic diseases that will allow us to infer which underlying mechanisms are causing an individual’s pain, so that treatment(s) can be appropriately directed. The pain field has moved well past the point where we can consider all individuals with RA, SLE, OA—or any chronic pain state, for that matter—to have the same underlying mechanism of pain and other somatic symptoms they experience. All of these symptoms are experienced in the brain. So, as a field, we need to better understand the brain in order to better treat our patients’ pain.

Identifying subsets of OA, SLE, and RA patients with prominent CNS factors might also help explain a longstanding conundrum in our fundamental understanding of these disorders. Disease models in OA, RA, and SLE are incomplete because peripherally based models do not explain a tremendous amount of variance in pain, fatigue, sleep, memory problems, and functional disability that is not accounted for by peripheral factors alone. For example, although the pathologic focus in OA is the joint and surrounding structures, multifocal pain in areas not affected by OA is common in patients with knee OA (120). Similarly, other somatic symptoms not explainable by a purely peripheral problem are often seen. For example, studies show fatigue to be a prominent problem in individuals with knee OA, and in many individuals, it is a more functionally limiting symptom than the pain (121). The current peripherally based theories regarding the pathogenesis of OA, SLE, and RA simply do not explain why these other somatic symptoms are so common and are often refractory to standard, peripherally based therapies.

## Conclusions

Chronic pain is an important component of many rheumatic diseases. One current limitation is the ability to identify patients in routine clinical settings who have greater contributions from centrally mediated



mechanisms. Practical evidence-based strategies need to be developed that will more readily identify these patients at the point of care as well as in the context of randomized clinical trials that include pain as an outcome measure. Centrally targeted therapies have the potential to change the treatment of chronic pain in many diseases. Several classes of centrally acting agents (e.g., tricyclics, SSNRIs, gabapentinoids) may prove to be more effective in individuals with rheumatic disorders who have a central pain overlay than classes of drugs that are typically more effective for peripherally based nociceptive pain states (e.g., NSAIDs), but additional studies are needed to prove this. Newly developed pain cohort studies should identify these subsets of RA, SLE, and OA patients who are preferentially predisposed to respond to these centrally, in addition to peripherally acting treatments, including nonpharmacologic therapy. There are few published results examining the role of combination therapy in chronic pain, but it is likely that such regimens will improve outcomes to the extent that they are influenced by multiple distinct mechanisms. These future studies will direct the development of new therapeutic options for millions of individuals with painful rheumatic disorders.

#### AUTHOR CONTRIBUTIONS

Drs. Phillips and Clauw drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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