Pain Mechanisms in Patients with Rheumatic Diseases

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KEYWORDS

• Nociplastic • Central sensitization • Rheumatic pain • Pain mechanisms

KEY POINTS

- Pain in rheumatic disorders can occur via any combination of 3 mechanisms: nociceptive pain (tissue damage and inflammation), neuropathic pain (nerve damage and dysfunction), and a new category of pain—nociplastic pain.
- Nociplastic pain (best exemplified by fibromyalgia) often is superimposed on and is independent of the other 2 mechanisms.
- Nociplastic pain is driven by the central nervous system, especially involving augmented pain and sensory processing.
- In the rheumatic diseases, ongoing nociceptive input can cause central sensitization, or nociplastic pain. This component of pain is less likely to respond to medications that treat nociceptive pain.

INTRODUCTION

Pain in the rheumatic diseases traditionally has been characterized as solely nociceptive, implying that targeting inflammation should manage rheumatic pain effectively. Despite therapeutic advancements providing excellent control of inflammation, however, patients continue to have pain. It is now known that pain is complex, with varying components of nociceptive, neuropathic, and a new type—nociplastic—pain, which is driven by augmented central nervous system (CNS) processing. These can occur in isolation, or represent a mixed pain picture, with substantial overlap in mechanisms.

Nociceptive Pain

Nociceptive pain results from tissue damage caused by trauma, nonhealing injury, or inflammatory processes. It is the primary type of pain in patients with rheumatic diseases and musculoskeletal disorders with underlying structural pathology.[1]

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Neuropathic Pain

Neuropathic pain typically is manifested as electric shock-like, lancinating, aching, numbing, burning, or tingling sensations that are distinct from nociceptive pain. It is the direct result of lesions or diseases of the somatosensory nervous system.[2]

Peripheral and Central Sensitization

When activated by noxious stimuli, local nociceptors secrete hundreds of inflammatory and proalgesic signaling molecules and convert to nerve signals in first-order somatosensory Aδ-nociceptor and C-nociceptor afferent terminals in the periphery. These nerve signals then are transmitted via specialized nerve fibers to the dorsal horn of the spinal cord and ascending cortical pathways to the brain.[3,4] Chemical mediators and neuropeptides are released and reduce the threshold for nociceptor neurons to generate action potentials, leading to amplified responsiveness and ultimately heightened pain sensitivity—termed, *peripheral sensitization*.[5]

This is a local, self-limited, protective mechanism and resolves as tissues heal and inflammation recedes.[6] If the stimuli are prolonged, neuroplastic changes of the nociceptors in the CNS at spinal and/or supraspinal levels occur; this is termed, *central sensitization*.[7,8]

Nociplastic Pain

The International Association for the Study of Pain now has referred to centralized pain as nociplastic pain.[9] Symptoms originate from augmented CNS pain and sensory processing and it is mechanistically different from nociceptive or neuropathic pain (**Table 1**). Hallmarks are diffuse hyperalgesia (increased pain to normally painful stimuli) and allodynia (pain to normally nonpainful stimuli). Along with chronic widespread pain (CWP), CNS-derived symptoms, for example, fatigue, mood disturbances, cognitive dysfunction, memory issues, and nonrestorative sleep, can occur. Perceptual amplification of auditory stimuli, along with increased sensitivity to complex visual stress light and unpleasant odors, also are noted; the auditory and visual sensitivities often are correlated with pain sensitivity in these patients.[10]

Nociplastic Pain Syndromes

A wide spectrum of pain disorders has been identified, with varying degrees of the contribution of nociplastic mechanisms.[11] The National Institutes of Health recently coined the term, *chronic overlapping pain conditions* (COPCs), to characterize the nociplastic pain syndromes, including fibromyalgia (FM), chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis, vulvodynia, endometriosis, chronic migraine and tension-type headache, nonspecific chronic low back pain, and temporomandibular disorders.[12] Pain may be activated by no identifiable inputs or normally benign inputs, with no particular abnormalities found on clinical examination, laboratory tests, and imaging.

Endophenotypes of Central Sensitization

COPCs are the prototypical example of a top-down, centralized pain state. The augmented pain and sensory processing in the CNS are characterized by a lifelong history of multifocal pain, multiple chronic pain conditions, high rates of comorbid symptoms, and familial predominance. Psychological contributors, such as depression and anxiety, are top-down sensitizers. Because emerging evidence suggests that therapies that work best for peripheral, nociceptive pain (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], opioids, injections, and surgical procedures) are less

Table 1
Mechanistic characterization of pain

	Nociceptive	Neuropathic	Nociplastic
Cause	Inflammation or damage	Nerve damage or entrapment	CNS or systemic problem
Clinical features	Pain is well localized, consistent effect of activity on pain	Follows distribution of peripheral nerves (ie, dermatome or stocking/glove), episodic, lancinating, numbness, tingling	Pain is widespread and accompanied by fatigue, sleep, memory, and/or mood difficulties as well as history of previous pain elsewhere in body
Screening tools		painDETECT	Body map or FM survey
Treatment	NSAIDs, injections, surgery, ? opioids	Local treatments aimed at nerve (surgery, injections, topical) or CNS-acting drugs	CNS-acting drugs, nonpharmacological therapies
Classic examples	OA Autoimmune disorders Cancer pain	Diabetic painful neuropathy Postherpetic neuralgia Sciatica, carpal tunnel syndrome	FM Functional gastrointestinal disorders Temporomandibular disorder Tension headache Interstitial cystitis, bladder pain syndrome

Variable degrees of any mechanism can contribute in any disease.

Chronic pain can originate from 3 different sources: peripheral nociceptive input, such as damage or inflammation of tissues; nerve damage and dysfunction in neuropathic pain; and nociplastic pain with central spinal and supraspinal mechanisms. The central factors can be best thought of as volume control or pain setting on what happens to peripheral nociceptive input.

likely to be effective in these individuals,[13] it is important to address these contributors.

Bottom-up, central sensitization is driven by persistent nociceptive input.[14] **Fig. 1** highlights the distinctions. Recent studies have demonstrated that 18% to 24% of patients with inflammatory arthritis meet criteria for FM.[15] These estimates likely underestimate the co-occurrence of nociplastic pain in the form of subthreshold FM that commonly is seen and is associated with the characteristic clinical, quantitative sensory testing (QST), and neurobiological features of FM.[16,17] This does not mean that ongoing peripheral nociceptive input is not contributing to an individual's pain; instead, pain mechanisms are considered additive. Even COPCs can be mixed pain states, with components of all 3 mechanisms.

RISK FACTORS

The complex interaction of biologic, psychological, and behavioral mechanisms plays a prominent role in pain and symptom expression in all rheumatic diseases and complicates their treatment. For example, in rheumatoid arthritis (RA) and osteoarthritis (OA), education level, coping strategies, and socioeconomic variables account for more of the variance in pain and disability than joint narrowing or erythrocyte sedimentation rate.[18]

Mood

There is a strong bidirectional link between mood disorders and persistent pain. Rheumatic diseases have a high rate of comorbid depressive symptoms, ranging from 8% to 75% in a recent review.[19] Depression, anxiety, and negative affect, are the most

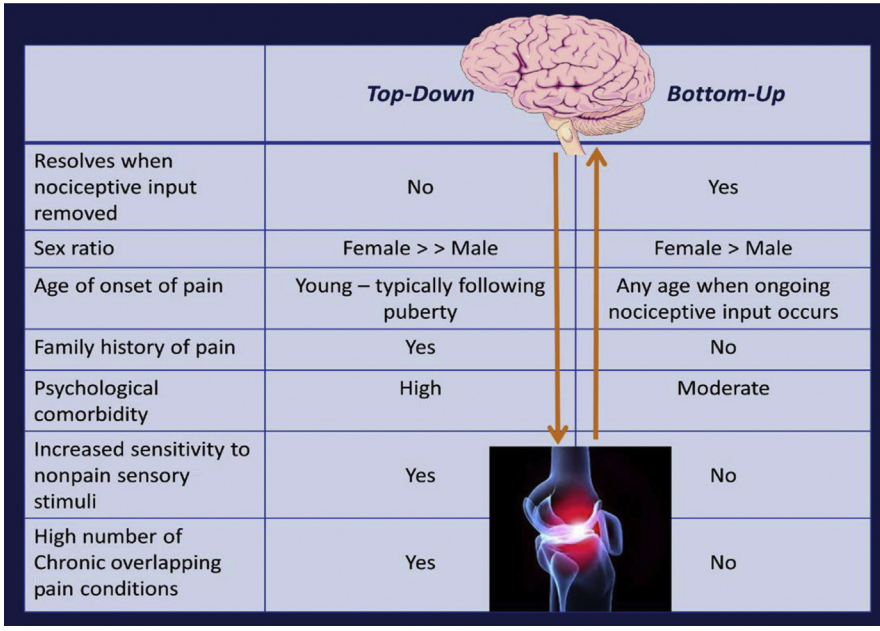

Fig. 1. Differences between top-down and bottom-up forms of central sensitization. (*Adapted from* Harte, SE, Harris, RE, Clauw, DJ. The neurobiology of central sensitization. J Appl Behav Res. 2018; 23:e12137.)

potent and robust predictors of the transition from acute to chronic pain.[20] and are strongly associated with persistent pain, physical disability, and mortality, more so than even pain intensity.[21]

Environmental Stressors and Trauma

COPCs are found in higher rates in individuals who have had certain infections (eg, Epstein-Barr virus, Lyme disease, Q fever, and viral hepatitis), and physical trauma (eg, motor vehicle collision). It often is challenging to attribute any single exposure (eg, in medicolegal) to the development of COPCs, because there often are preexisting or co-occurring stressors. A majority of patients return to their baseline health. Tenuous housing, employment status, low educational levels, and low family income have been associated with chronic pain; financial or housing insecurity–related stress may promote aberrant pain processing.[22]

Adult veterans, combat exposure, and posttraumatic stress disorder have strong statistical associations with chronic pain and transition from acute to chronic pain.[23,24] Psychological, sexual, or physical abuse is associated with a 2-fold to 3-fold increase in the development of CWP; in a recent meta-analyses,[23] childhood abuse conferred a 97% increase in risk for having FM or COPCs in adulthood.[23]

Cognitive Factors

Catastrophizing is a cognitive and emotional response to pain consisting of magnification, rumination, and helplessness about the ability to manage pain (eg, "This is the worst pain," "I can think of nothing else," and "There's nothing I can do"). It is the single most significant pretreatment risk associated with poor treatment outcomes for pain-relieving interventions. It is associated with enhanced anterior insular cortex activation on functional magnetic resonance imaging (fMRI) and frequently co-occurs with maladaptive behaviors, for example, fear of movement.

Social Support

In patients with chronic pain conditions, broad social support has been associated with improved functioning. In contrast, high levels of solicitous responses of parents or partners have been linked with higher pain intensity and pain-related disability.

Racism

As race has been moved away from being considered genetics-based to a social construct that captures the impacts of racism,[25] several studies increasingly have found that racial discrimination is significantly related to pain intensity and severity in African American groups.[26]

Sleep

Inadequate or interrupted sleep results in impaired inhibitory mechanisms; poor sleep is a strong predictor of subsequent pain and is noted in 90% of FM patients. Pain and abnormal sleep are cyclical and cumulative, and the severity of sleep disturbance correlates with pain severity, reduced pain inhibition, and fatigue.[27] In studies, nonrestorative sleep was the strongest predictor of CWP.

Lifestyle Factors

Physical inactivity is a risk factor for the development of chronic pain and may alter the CNS exaggerate responses to low-intensity muscle insults. Smoking and consumption of high-fat foods have been linked to hyperalgesia.

Resilience and Protective Factors

Historically, the factors have been studied that make it more likely to develop pain but little attention has been paid to factors that might be protective. In many studies across many diseases, the presence of these protective factors often more powerfully predicts who will not develop chronic pain than negative factors predict who will. For example, positive affect and optimism are associated with lower pain sensitivity, lower pain intensity, and less dysfunction[28] Positive affect is thought to be a mediator of resilience, lowering pain catastrophizing, and may buffer maladaptive pain-related behaviors, such as fear of movement. Positive affect is surprisingly highly malleable; encouraging behavioral activation (having patients schedule and perform things they find enjoyable), aimed at raising positive feelings, cognitions, and behaviors rather than reducing negative ones, has shown large effect sizes with mood and improvements with chronic pain.

Encouraging lifestyle modification, cognitive-behavior therapy, and mind-body techniques, such as mindfulness, have been shown to have beneficial effects on chronic pain and pain-related outcomes. These techniques can improve patients' self-efficacy—individuals' belief in their ability to perform a behavior or achieve the desired outcome. This determines thoughts, feelings, and behaviors in stressful situations and affects the ability to successfully cope when confronted with challenges, specifically to increase pain self-efficacy.

Pain-related expectations also influence the experience of pain as well as treatment outcome, and learning active coping techniques (ie, techniques used to control pain or continue functioning despite the pain) is associated with positive outcomes, including positive affect, better psychological adjustment, and decreased depression.[21]

MECHANISTIC STUDIES

Quantitative Sensory Testing

QST is a method that identifies abnormalities in pain mechanisms by assessing pain in response to quantifiable noxious stimuli[29] and has been used in most early studies of nociplastic pain conditions. Data from QST studies suggest a wide, bell-shaped distribution in pain sensitivity across the general population.[30,31] Individuals with nociplastic pain syndromes fall on the right side of the curve, noting diffuse hypersensitivity in both at and outside the region of injury (ie, secondary hyperalgesia and allodynia).[30,32] This type of testing can be mechanistically elucidating in rheumatology, where disease measures for example, the Clinical Disease Activity Index (CDAI), which includes subjective components, for example, tender joint count (TJC) and patient global assessments (PGAs), may reflect higher disease inaccurately activity by underestimating the role of nociplastic pain.

Individuals with nociplastic pain are noted to have descending inhibitory pain pathways that do not function appropriately, as measured by conditioned modulation paradigms (CPMs). Impaired CPM also has been shown in RA patients with nociplastic pain, which may be mediated by sleep disturbances.[33]

Temporal summation (TS) is the clinical measure of windup—the progressive summation of C-fiber responses in response to repetitive noxious stimuli, leading to increased firing of the dorsal horn, leading to increasing perceived pain intensity.[34] This normal response, which occurs in healthy individuals, is enhanced in central sensitization and is predictive of individuals who will respond poorly to peripheral pain interventions.

The pain threshold is defined as the point at which a particular sensation first becomes painful. In studies of stable RA patients on disease-modifying antirheumatic

drugs treatment, low pressure pain thresholds (PPTs) (high pain sensitivity) were associated with higher TJC, worse PGA, higher depression, and higher FM scores.[35] Lee and colleagues[17] demonstrated high pain sensitivity (low PPTs and high TS) was associated with high CDAI scores, supporting the role of nociplastic pain in RA.

QST studies have shown that FM patients are just as hyper-responsive to auditory, visual, and other sensory stimuli as they are to pain and that this is a key feature of this pain mechanism. The brain regions that are known to be hyperactive in nociplastic pain, for example, the insula, are involved in the processing of all sensory stimuli, not just painful stimuli.

Functional Brain Imaging Studies

Functional, structural, and chemical functional brain imaging studies have enriched the understanding of the rheumatic disease pain mechanisms. They allow assessment of activity at rest as when individuals are given stimuli (ie, evoked scans), and when used in combination in the same individual much can be gleamed regarding underlying neural mechanisms.

For instance, the insula consistently is hyperactive and likely to play a key pathogenic role. The insula displays differentiation; the posterior serves a purer sensory role, and the anterior is associated with the emotional processing of sensations.[36] The connectivity between the insula and the default mode network (DMN) (a group of interconnected brain regions, including the medial prefrontal cortex, posterior cingulate cortex, precuneus, inferior parietal lobule, hippocampal formation, and lateral temporal cortex) has attracted particular attention in recent years.[37] In healthy subjects, insula activity has no correlation with DMN regions. In chronic pain disorders, insula subregions can become functionally connected with the DMN; the degree of hyper-connectedness is related to ongoing pain severity.[38]

When individuals with FM are given a mild pressure or heat stimuli that most individuals feel as touch rather than pain, they experience pain and activation in pain-processing brain regions.[39,40] During a painful stimulus, connectivity is decreased between key anti-nociceptive regions (eg, the brainstem—the origin of descending analgesic pathways) and a brain region identified as a potential source of dysfunctional pain inhibition in FM.[41] Neuroimaging has confirmed QST studies that these individuals are more sensitive to several sensory stimuli other than pain, and machine learning paradigms can distinguish FM from non-FM patients accurately, with more than 90% accuracy using these results.[42,43]

Other neuroimaging techniques have been used to assess the levels of neurotransmitters and chemical mediators involved in driving nociplastic pain. Proton magnetic resonance spectroscopy can identify levels of excitatory neurotransmitters, for example, glutamate that typically are elevated in brain regions in FM,[43,44] Pregabalin and gabapentin work by reducing glutamatergic activity. Individuals with the highest pretreatment levels of glutamate in the posterior insula were those most likely to respond to pregabalin; the clinical response was associated with normalization of fMRI and connectivity findings.[44,45] Conversely, low levels of 1 of the body's major inhibitory neurotransmitters, γ-aminobutyric acid (GABA),[46,47] have been seen. This likely accounts for the effectiveness of GABAergic drugs, such as γ-hydroxybutyrate, in a subset of individuals with FM[48] and the observation that low amounts of alcohol might protect against the development of nociplastic pain.[49,50]

PET can examine binding of neurotransmitters in the CNS. A series of studies have found evidence of decreased mu-opioid receptor availability and increases in endogenous opioids in the cerebrospinal fluid of FM patients[51]—likely why opioids appear

ineffective in FM. PET also recently has been used to identify possible evidence of glial cell activation in FM.[52]

Fig. 2 illustrates the neurotransmitters that have been demonstrated to influence pain transmission in the CNS. This neurochemical profile helps illustrate why no single class of CNS analgesia is likely to work in every patient with pain of CNS origin.

fMRI supports evidence that pain and depression largely are independent but overlapping physiologic processes in nociplastic pain. In FM, comorbid depression has been correlated with increased activity in the affective or motivational aspects of pain processing (mainly unpleasantness) regions—anterior insula and amygdala activations[53] but not associated with lateral brain structures involved in the sensory processing of pain (ie, location and intensity of the pain).

fMRI studies also have noted decreased activation in regions of the brain involved in sensory and emotional pain processing within 24 hours of tumor necrosis factor (TNF)-α inhibition in RA patients, potentially explaining the immediate pain relief noted.[54,55] Similar to other chronic pain syndromes, depressive symptoms in RA have been associated with activation of the medial prefrontal cortex[56] involved in emotional processing.

Genetics

The strong familial predisposition to nociplastic pain syndromes has prompted the search for specific genetic polymorphisms associated with pain processing. The

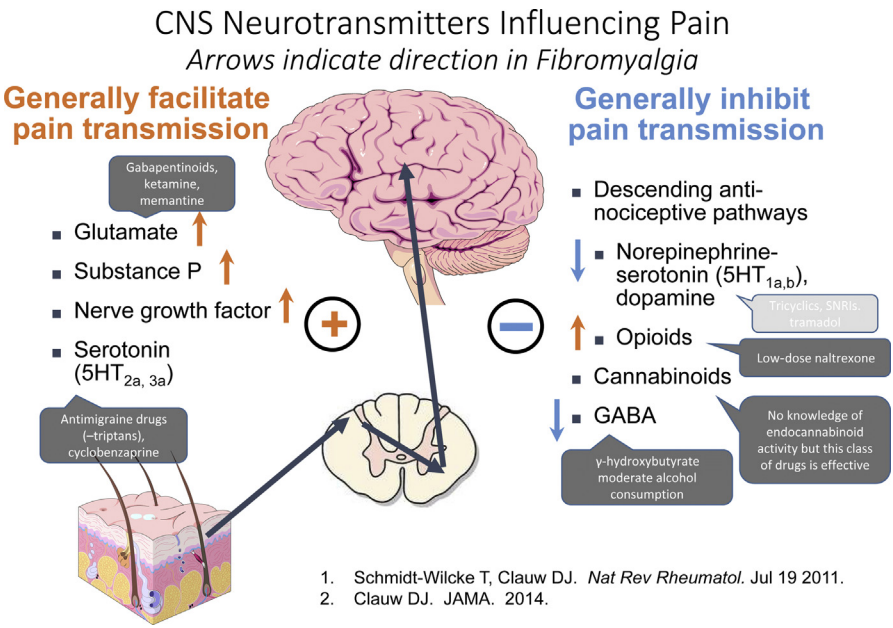

Fig. 2. Neurotransmitter systems that generally facilitate (*left*) or inhibit (*right*) CNS pain transmission. The arrows indicate the levels of these neurotransmitters in the CNS of individuals with FM, and the boxes indicate drugs that have been shown to be effective in FM that likely are working in part via those neurotransmitters. SNRI, serotonin-norepinephrine reuptake inhibitor. (Clauw, 2014; Schmidt-Wilcke and Clauw, 2011). (*Adapted from* Harte, SE, Harris, RE, Clauw, DJ. The neurobiology of central sensitization. J Appl Behav Res. 2018; 23:e12137.)

serotonin 5-HT2A receptor polymorphism T/T phenotype, serotonin transporter, dopamine-4-receptor, and catecholamine *O*-methyltransferase (COMT) polymorphisms all noted were in higher frequency in FM patients than controls, although this has not been replicated in subsequent studies.[57] The COMT gene encodes the enzyme believed to moderate the transmission of pain signals via the removal of catecholamine (ie, dopamine, epinephrine, and norepinephrine); reduced COMT activity appears to be related to increased pain sensitivity.[58] Currently, hundreds of genes thought to be relevant to human pain perception or analgesia have been identified, include the genes encoding voltage-gated sodium-channels (Nav), GTP cyclohydrolase 1, mu-opioid receptors, and various genes of the dopaminergic, glutamatergic, and GABAergic pathways.[59] Because environmental factors, for example, stress, influence pain pathogenesis, the role of epigenetics is being investigated.[60] Initial findings from chronic pain models suggest that chromatin structure alterations may trigger gene expression to promote the evolution from acute pain to central sensitization.[61]

The Role of Neuroendocrine or Autonomic Abnormalities

Because of this link between exposure to stressors and the subsequent development of nociplastic pain syndromes, the human stress systems have been studied extensively in this condition.[62] There have been inconsistencies in findings, and now it is posited that alterations of the hypothalamus-pituitary-adrenal (HPA) axis might represent a diathesis or be due to pain or early life stress, rather than causing it.

In 2 studies examining HPA function in FM, McLean and colleagues[63] showed that salivary cortisol levels varied with pain levels and that cerebrospinal fluid levels of

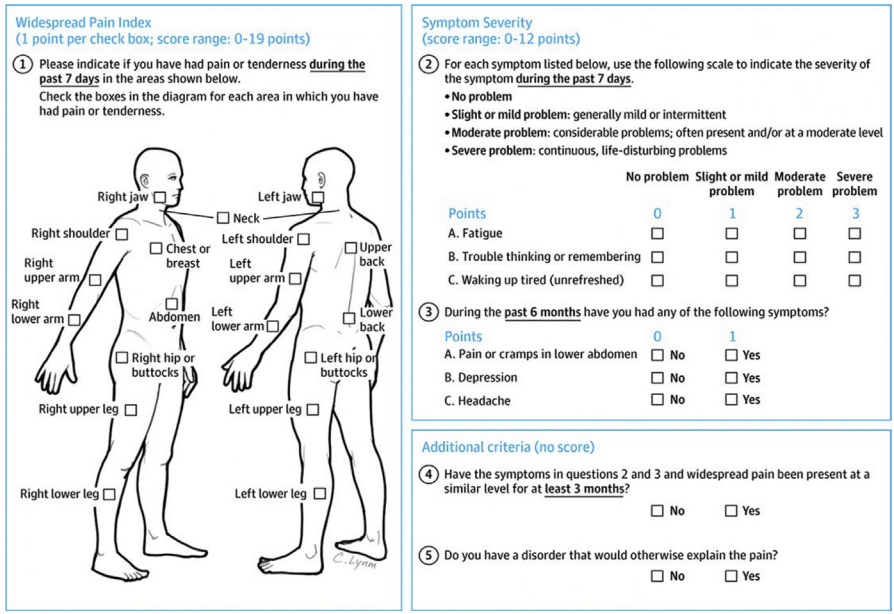

Fig. 3. The 2011 survey criteria for fibromyalgia (Wolfe and colleagues, 2011) using the Michigan Body Map (Brummett and colleagues, 2016). (*Adapted from* Harte, SE, Harris, RE, Clauw, DJ. The neurobiology of central sensitization. J Appl Behav Res. 2018; 23:e12137.)

corticotropin-releasing factor were related more closely to an individual's pain level or a history of early-life trauma than whether they were an FM case or control.

Evidence of Abnormal Cytokines and Immune Dysfunction in Nociplastic Pain

Although nociplastic pain is not thought to be autoimmune in nature, data suggest the immune system may be playing some role.[64] Multiple inhibitory transmitters act at the spinal level to reduce the volume of pain transmission, for example, serotonin, norepinephrine, enkephalins, dopamine, and GABA.

Animal models have found receptors for TNF-α, interleukin (IL-1β), and IL-17 on sensory neurons[65] and transmembrane signal-transducing subunit on the dorsal root ganglion neurons that binds to the IL-6/IL-6 receptor complex.[66] The most consistent finding noted to date is a mild elevation in IL-8, which is a cytokine associated with autonomic dysfunction; it could be related to the dysautonomia seen in some patients.[67] The roles of diet, obesity, and microglial involvement are being investigated actively.

The Role of Small Fiber Neuropathy in Nociplastic Pain

Although several groups have shown evidence of decreased intraepidermal nerve fiber density (ie, small fiber neuropathy) in FM,[68–71] the pathologic significance is unclear.[72] Reduced nerve fiber density is nonspecific, has been noted in more than 50

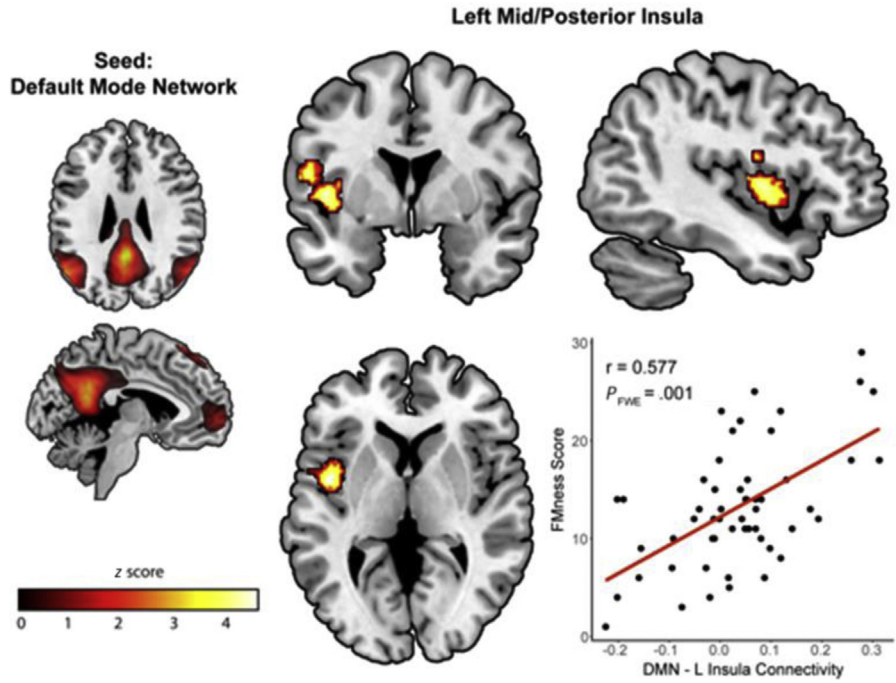

Fig. 4. Increased brain connectivity between the DMN and left mid/posterior insula in RA patients is associated with fibromyalgianess. Scatterplots show positive correlations for interindividual differences in brain connectivity (Fisher-transformed r values) with the total fibromyalgianess score. FEW, family-wise error. (*From* Basu N, Kaplan CM, Ichesco E, et al. Neurobiologic Features of Fibromyalgia Are Also Present Among Rheumatoid Arthritis Patients. Arthritis & Rheumatology. 2018;70(7):1000-1007.)

different pain and nonpain conditions,[72] and is reproducible in animal models of central sensitization, by increasing insular glutamate.[73] Reduced nerve fiber density likely reflects an adaptive structural and functional reorganization of the PNS in the context of ongoing chronic pain and neurologic conditions.

THE CONTINUUM OF FIBROMYALGIA TO FIBROMYALGIANESS

Wolfe[14] was the first to describe the concept and clinical importance of "fibromyalgianess" by showing that "subthreshold" FM amplifies the symptom severity in patients with rheumatologic and classically nociceptive diseases. In a series of studies, he showed that in individuals with conditions, such as RA, low back pain, and OA, an individual's FM score, derived with measures similar to the American College of Rheumatology 2010/2011/2016 FM criteria,[74] was more predictive of pain and disability than more objective measures of activity of these illnesses, such as measures of inflammation or joint damage.[75]

The entirely self-reported survey version assesses the Widespread Pain Index (up to 19 body areas each counted as 1 point) and the Symptom Severity Index (that queries

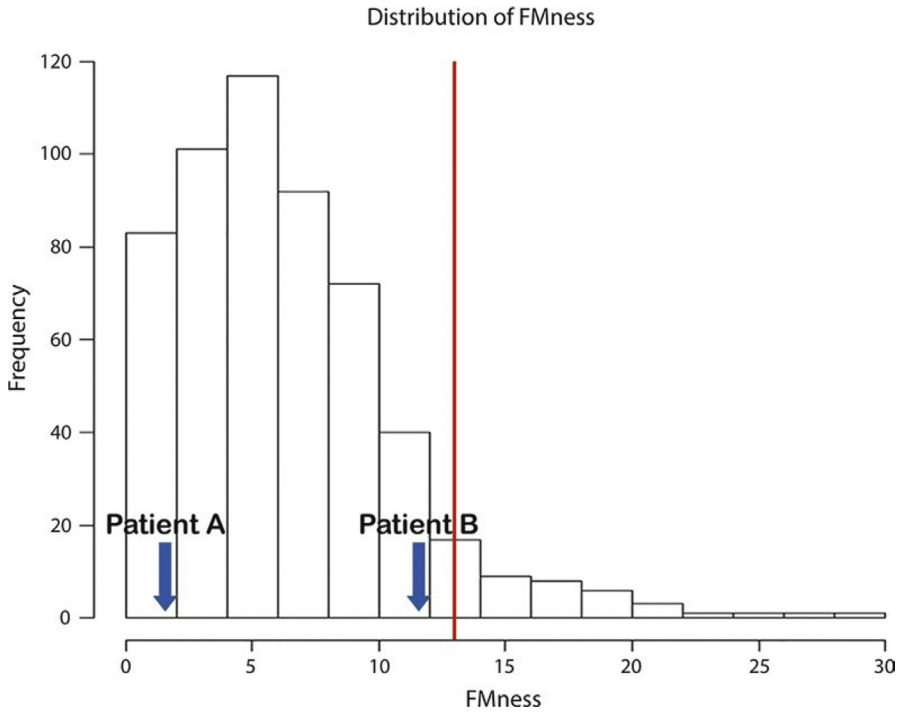

Fig. 5. Distribution of fibromyalgianess (FMness). FMness scores from individuals undergoing lower extremity arthroplasty for OA (Brummett and colleagues, 2013; Brummett and colleagues, 2015). The red line indicates the score meeting FM criteria. Two different hypothetical participants, without FM, are compared with respect to the amount of oral morphine equivalents required for pain control at 24 hours to 48 hours and the likelihood of achieving 50% improvement in pain at 6 months. Compared with Patient A with localized pain and no somatic symptoms, Patient B would need 90 mg more oral morphine equivalents during the first 48 hours of hospitalization, and is 5-times less likely to have a 50% improvement in pain at 6 months. (*Adapted from* Harte, SE, Harris, RE, Clauw, DJ. The neurobiology of central sensitization. J Appl Behav Res. 2018; 23:e12137.)

the presence and severity of fatigue, sleep disturbances, memory difficulties, each scored 0–3 for presence and severity) as well as irritable bowel, headaches, and mood problems (1 point each; total Symptom Severity Index score = 0–12). They are combined for a total FM score of 0 to 31, with a score of 13 as diagnostic of FM (Fig. 3).

The higher the score, the more nociplastic pain is contributing to patients' symptoms[14] and the more likely simply treating the nociceptive portion of the pain is not sufficient. This is supported further by a recent fMRI study by Basu and colleagues,[16] which found that increased connectivity between the DMN and the insula—the most consistently found feature of centralization in nociplastic pain syndromes—also was seen in RA patients with high degrees of fibromyalgianess (Fig. 4).

In a study by Brummett and colleagues, patients scheduled for hip or knee replacements or hysterectomies completed the 2011 FM survey criteria. For each 1-point increase in baseline FM score, individuals needed more morphine and had a 17.8% increase in the odds of failure to meet the threshold of 50% improvement in pain. This held true whether the score increased from 2 to 4 or from 12 to 14 (the latter score moving the individual into an FM diagnosis) (Fig. 5).

Recognizing superimposed nociplastic pain on top of nociceptive or neuropathic pain is essential, because the centralized component requires different treatment; peripherally directed treatments are not effective.

CLINICS CARE POINTS

- Many patients present with mixed pain states, with components of nociceptive pain, neuropathic pain, and nociplastic pain—or any combination of all 3.
- In addition to biologic and mechanical factors, psychological and behavioral mechanisms play a prominent role in pain and symptom expression in all rheumatic diseases and can have an impact on their treatment.
- Identifying potentially modifiable risk factors, such as physical inactivity and sleep, and enhancing protective factors, such as positive affect and optimism, can have beneficial effects on chronic pain and pain-related outcomes.
- Optimal management for clinicians treating patients with chronic pain is based on targeting the underlying mechanisms of pain and tailoring the management modality using a multimodal approach.

DISCLOSURE

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