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SPECIAL ISSUE ON CENTRAL SENSITIZATION

The neurobiology of central sensitization

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Abstract

Central sensitization refers to the amplification of pain by central nervous system mechanisms. Classically described as a consequence of ongoing nociceptive input, it is increasingly recognized that central sensitization also occurs independent of peripheral injury or inflammation. Features of central sensitization have been identified in nearly all chronic pain conditions, and it is considered the primary underlying cause of pain in conditions such as fibromyalgia. Central sensitization is characterized in these conditions by widespread pain and multisite hyperalgesia/allodynia. Co-occurring symptoms include fatigue, mood and cognitive problems, sleep disturbances, and multisensory hypersensitivity. Individuals with central sensitization often report previous exposure to psychosocial or physical stressors, and a higher personal lifetime and family history of pain, with the latter findings supported by genetic studies. Neuroimaging studies of central sensitization show evidence of: changes in brain gray matter in pain processing regions; neurochemical imbalances; and altered resting brain-network connectivity between pronociceptive and antinociceptive brain areas. Immune system abnormalities have also been demonstrated in individuals with central sensitization. The recognition of central sensitization, and whether it is being driven by ongoing nociceptive input or it is occurring in the absence of a peripheral driver, is critical for effective pain management.

1 | INTRODUCTION

In this Special Issue of JABR, Woolf (2018) describes the first use of the term "central sensitization" as it relates to pain processing, as well as the early evolution of the meaning of this term. Described initially only in animal models, the term was first used by Woolf to refer to a specific spinal disorder mechanism that was responsible for augmenting ongoing peripheral nociceptive input (Woolf, 1983). Other preclinical pain researchers subsequently identified additional spinal mechanisms that amplify nociceptive signaling. The hallmarks of these processes were the presence of hyperalgesia and/or allodynia on quantitative sensory testing (QST) in animal models of nociception, often accompanied by enlargement of the nociceptive field and/or electrophysiological evidence of decreased firing threshold and increased discharge of spinal nociceptive neurons. Thus, the term central sensitization began to be used in a broader sense to convey the notion that an array of spinal mechanisms may be involved in amplifying or maintaining peripheral nociceptive input (Dougherty, Palecek, Paleckova, Sorkin, & Willis, 1992; Sluka & Westlund, 1992; Treede, Davis, Campbell, & Raja, 1992; Willis, 1988). Even though a substantial body of research had begun to demonstrate the important role for supraspinal mechanisms in pain processing (Gebhart, 1986; Jensen & Yaksh, 1992; Willis, 1985; Yaksh, 1988), in the 1980s and early 1990s, the term central sensitization was originally applied: (a) only to situations where there was some initial ongoing peripheral nociceptive input; and (b) where the underlying mechanism(s) of this phenomenon was thought to lie in the spinal cord and dorsal root ganglion.

In the mid-1990s, many investigators began to leverage the term and concept of central sensitization as a way of explaining the pain hypersensitivity observed in a number of chronic pain states in humans, including neuropathic pain (Gracely, Lynch, & Bennett, 1992; Persson, Axelsson, Hallin, & Gustafsson, 1995); fibromyalgia (FM) (Anderberg, 2000; Gibson, Littlejohn, Gorman, Helme, & Granges, 1994; Granges & Littlejohn, 1993; Kosek, Ekholm, & Hansson, 1995; Sorensen, Bengtsson, Backman, Henriksson, & Bengtsson, 1995); headache (Jensen, Rasmussen, Pedersen, Lous, & Olesen, 1992; Jensen, Rasmussen, Pedersen, & Olesen, 1993); temporomandibular disorder (TMD) (Fillingim, Maixner, Kincaid, Sigurdsson, & Harris, 1996); and irritable bowel syndrome (IBS) (Mertz, Naliboff, Munakata, Niazi, & Mayer, 1995). As with the animal models, the original technique used to identify central sensitization in humans was QST. These early QST studies typically noted the same findings of secondary hyperalgesia or allodynia seen in animal models of central sensitization, and this was used to infer that these same underlying processes may be playing a role in humans with these chronic pain conditions.

More recently, newer techniques, such as functional, chemical, and structural brain imaging, EEG, and other research techniques, have been used to substantiate and further identify the presence of, and underlying mechanisms driving, central sensitization. Central sensitization has now been suggested to play a role in hundreds of painful and other medical conditions. In fact, so much has been learned about the ubiquity of this problem in populations of chronic pain patients that there is now widespread consensus in the pain field that this might represent a third underlying core mechanism for pain, above and beyond nociceptive and neuropathic pain mechanisms that have been recognized for some time (Brummett, Clauw et al., 2016; Kosek et al., 2016).

Chronic pain conditions that are now recognized mechanistically to fall within the spectrum of central sensitization include: FM; IBS (previously termed "spastic colitis" until the recognition that there was little "–itis" and that motility changes were not the major pathological feature); TMD (previously termed temporomandibular joint syndrome until it was recognized that the problem was largely outside the joint) (Bair, Brownstein, et al., 2013; Bair, Ohrbach, et al., 2013; Fillingim et al., 2011; Greenspan et al., 2013); and urinary chronic pelvic pain syndromes (where, again, the condition previously called interstitial cystitis is now called bladder pain syndrome) (Bagarinao et al., 2014; Clemens et al., 2014; Farmer et al., 2015). This is not to say peripheral factors, or low-grade inflammation that is not identifiable clinically, do not play some role in these entities. But it is relevant that clinicians who care for individuals with these conditions, and who are quite adept at identifying (with blood tests, imaging, or endoscopy) peripheral damage or inflammation, have generally concluded that these are not inflammatory or

peripheral-based disorders. A recent term, *Chronic Overlapping Pain Conditions* (COPCs), has been coined by the NIH to indicate that FM, IBS, chronic fatigue syndrome (CFS), headache, interstitial cystitis/bladder pain syndrome, TMD, endometriosis, low back pain, and dry-eye disease may all represent conditions with overlapping clinical and pathophysiological features (i.e., those related to central sensitization), where central factors may be playing a prominent or exclusive role in their pathogenesis (Levitt et al., 2017; Maixner, Fillingim, Williams, Smith, & Slade, 2016). Most of the initial studies examining the pathophysiology of central sensitization in humans have been in conditions such as FM and other COPCs, because these were among the first conditions where prominent central factors were identified.

However, these same features suggesting central sensitization are also commonly seen in individuals with chronic pain conditions and illnesses *where there is clearly ongoing nociceptive input*. A subset of individuals with any chronic pain condition will display features of central sensitization, including individuals with autoimmune disorders, any type of arthritis, cancer, sickle cell disease, and hypermobility syndromes (Clauw & Witter, 2009; Darbari, Ballas, & Clauw, 2014; Gwilym et al., 2009; Henry & Clauw, 2012; Phillips & Clauw, 2013). Because these individuals with central sensitization clinically resemble individuals with FM, they were previously labeled as having "secondary fibromyalgia" in the rheumatological literature. This form of central sensitization has not been nearly as well studied mechanistically in humans, in part because most studies of COPCs purposefully excluded individuals with demonstrable peripheral disease. What is known about this type of central sensitization is that it seems to be at least in part driven by ongoing nociceptive input because, when the input is removed, the features of central sensitization partially or entirely remit (Gwilym, Filippini, Douaud, Carr, & Tracey, 2010; Kosek & Ordeberg, 2000; Staud, Weyl, Bartley, Price, & Robinson, 2014).

This present review will provide a broad overview of these aggregate studies describing the current understanding of central sensitization as observed in humans, as well as identify unresolved issues in this field.

2 | FEATURES OF CENTRAL SENSITIZATION

2.1 | Epidemiological and Observational Studies

Individuals who develop COPCs begin developing pain and other related central-sensitization symptoms (fatigue, sleep disturbance, sensory sensitivity) in early life. For example, individuals who eventually go on to develop FM are more likely to experience headaches, dysmenorrhea, TMD, chronic fatigue, IBS and other functional GI disorders, interstitial cystitis/painful bladder syndrome, endometriosis, and other regional pain syndromes (especially back and neck pain) (Aaron & Buchwald, 2001; Hudson & Pope, 1994). What often appears clinically as a new episode of acute or subacute pain is just the newest region of the body experiencing pain (Warren et al., 2009). Consequently, many pain experts have suggested that COPCs are best understood as a single lifelong disease that merely tends to manifest in different bodily regions over time (Tracey & Bushnell, 2009; Williams & Clauw, 2009; Woolf, 2011).

In addition to COPC, patients having a high personal lifetime history of pain, often have a strong family history of chronic pain. The first-degree relatives of FM patients are eight times more likely to have FM compared to family members of healthy controls, and they also report very high rates of other chronic pain conditions (Arnold et al., 2004). Furthermore, family members of individuals with FM are much more tender than the family members of controls, regardless of whether they have chronic pain or not (Buskila, Neumann, Hazanov, & Carmi, 1996; Hudson, Hudson, Pliner, Goldenberg, & Pope, 1985; Kato, Sullivan, Evengard, & Pedersen, 2006). This familial and personal coaggregation of conditions has been called many other terms prior to COPCs, including *affective spectrum disorder* (Hudson, Goldenberg, Pope, Keck, & Schlesinger, 1992) and, more recently, *central sensitivity syndromes* (Yunus, 2008), and *chronic multisymptom illnesses* (Yunus, 2008). The key symptoms besides pain that typically coaggregate together are fatigue, memory difficulties, and mood disturbances (Fukuda et al., 1997,

1998). Twin studies suggest that approximately 50% of the risk of developing these conditions is genetic, and 50% is environmental (Kato, Sullivan, Evengard, & Pedersen, 2009).

Environmental factors that are associated with the development of FM and other COPCs include various types of "stressors," that typically involve acute pain for at least a few weeks. Psychosocial stress, including childhood trauma, is but one such stressor. FM and other COPCs are found at much higher than expected rates in individuals who have experienced certain types of infections (Buskila, Atzeni, & Sarzi-Puttini, 2008 [e.g., Epstein Barr Virus, Lyme disease, Q fever, viral hepatitis]), physical trauma (e.g., motor vehicle collisions) (McLean et al., 2011), and deployment to war (Lewis, Wassermann et al., 2012). Of note, only 5%–10% of individuals exposed to these stressors develop FM or CFS; the overwhelming majority of individuals who experience these same infections or other stressful events return to their baseline state of health. It is also likely that part of the reason these different stressors can seemingly lead to worsening of central sensitization symptoms is because of how these stressors affect activity level, sleep, or overall distress, any of which then can lead to worsening of pain and other symptoms (Ablin et al., 2013; Arnson et al., 2007; Crook, Moldofsky, & Shannon, 1998; Moldofsky, 2010; Moldofsky, Saskin, & Lue, 1988). This may also be why treatments, such as exercise and improving sleep, seem to be so important and helpful in the overall treatment of patients with central sensitization.

As previously noted, the central sensitization or FM-phenotype is also commonly seen as a comorbidity in other chronic pain conditions such as osteoarthritis, rheumatoid arthritis, and systemic lupus erythematosus (SLE) (Buskila, Neumann, Vaisberg, Alkalay, & Wolfe, 1997; Buskila, Shnaider, et al., 1997; Clauw et al., 1997; McLean & Clauw, 2004). As many as 25% of patients correctly diagnosed with generalized inflammatory disorders such as SLE, rheumatoid arthritis, and ankylosing spondylitis will also meet the clinical criteria for FM (Clauw, 1995a,b). This rate is even higher in individuals with conditions such as chronic low back pain, sickle cell disease, Ehler's Danlos, and other hypermobilitiy syndromes. However, in clinical practice, this coexpression is often unrecognized, especially when central sensitization develops after the nociceptive or neuropathic condition is diagnosed. In this setting, when comorbid central sensitization goes unrecognized, patients are often unnecessarily treated more aggressively with peripherally direct interventions, such as surgery or immunosuppressive drugs, leading to increased morbidity without the desired therapeutic effects.

Fibromyalgia and other COPCs occur much more commonly in individuals with early life and current stress, and many if not most individuals will have a lifetime history of a psychiatric disorder such as depression or anxiety (Epstein et al., 1999). There is typically more psychiatric and psychological comorbidity seen in tertiary care settings or in individuals who are refractory to treatment. This bi-directional relationship between FM and psychiatric conditions is likely due in part to the fact that there are common triggers to both sets of conditions (e.g., early life stress or trauma), as well as shared pathophysiology (i.e., many of the neurotransmitters that affect pain transmission also affect mood, memory, fatigue, sleep). Other risk factors for developing FM that are potentially modifiable include poor sleep, obesity, physical inactivity, and poor job or life satisfaction. Similarly, cognitive factors, such as catastrophizing (the feeling that pain is very bad and associated with a poor prognosis for recovery) or movement-related fear, are poor prognostic factors in FM and other chronic pain states.

2.2 | Animal models

As noted above, all of the early animal models of central sensitization required ongoing nociceptive input to drive central sensitization. In fact, this was one of the hallmark features of central sensitization in these models, in that the observed processes seemed to lessen or disappear when the ongoing peripheral nociceptive input was removed or blocked. This led to the early view that aggressively reducing ongoing nociceptive input to block subsequent central sensitization (i.e., pre-emptive analgesia, Woolf, 1991) might be useful therapeutically. This general approach is still used, especially in perioperative medicine, where studies generally show that individuals with

lower pain scores during the acute painful episode have less subsequent features of central sensitization following surgery (although it is often difficult to disentangle *cause* vs. *effect* in these studies, because individuals with less central sensitization would be expected to have less pain to an acute stimulus).

More recent animal models of both somatic and visceral pain emphasize that these same features of central sensitization can occur without any ongoing nociceptive input. For example, although few would purport that there is an animal model that mimics all of the key clinical features of FM, animal models can nonetheless be very helpful in understanding the pathogenesis of this condition (Sluka, 2009; Sluka & Clauw, 2016). Animals can clearly develop the critical features of central sensitization without any ongoing nociceptive input, including when exposed to subchronic swim stress (Suarez-Roca et al., 2006); neonatal separation from their mothers (Pierce & Christianson, 2015); and many other nonpainful stimuli (DeSantana, da Cruz, & Sluka, 2013; Sluka, Kalra, & Moore, 2001). Features of central sensitization and animal pain-like behaviors consistent with diffuse pain are also seen when central nervous system (CNS) neurotransmitters are purposefully altered in the directions found in FM. For example, chronic reserpine administration (which depletes bioamines) leads to features consistent with central sensitization (Taguchi et al., 2015), as does directly increasing glutamate levels in the insulae (Watson, 2016). This latter model of increasing insular glutamate was recently reverse translated to show that findings of "small fiber neuropathy" could be induced simply by increasing CNS glutamate, as is known to occur in FM (Harte et al., 2017).

2.3 | Genetic factors

The strong familial predisposition to FM and other chronic pain conditions has led many to study specific genetic polymorphisms that may be associated with a higher risk of developing FM. First, candidate-gene studies showed that genetic findings, such as the serotonin 5-HT2A receptor polymorphism T/T phenotype; serotonin transporter; dopamine 4 receptor; and COMT (catecholamine *o*-methyl transferase) polymorphisms all were noted at higher frequency in FM patients than controls. Some subsequent studies confirmed certain of these associations, whereas others did not (Buskila, Sarzi-Puttini, & Ablin, 2007; Diatchenko, Fillingim, Smith, & Maixner, 2013). Subsequent larger genome-wide linkage and candidate-gene studies identified other putative targets (Arnold et al., 2013; Smith et al., 2012). The linkage studies confirmed the strong genetic contribution to FM, and suggested linkage of FM to the chromosome 17p11.2-q11.2 region. The large candidate gene study identified three genes—(GABRB3 [rs4906902, $p = 3.65 \times 10^{-6}$); TAAR1 (rs8192619, $p = 1.11 \times 10^{-5}$); and GBP1 (rs7911, $p = 1.06 \times 10^{-4}$) with single-nucleotide polymorphisms (SNPs)—that differed in frequency between FM patients and healthy controls (Smith et al., 2012). TAARI, along with several additional genes (RGS4, CNR1, and GRIA4) showed evidence of association with FM in a replication analysis using a second independent cohort of FM patients (Smith et al., 2012). In light of the fact that classic genetic studies have not yet identified strong, reproducible polymorphisms or haplotypes associated with FM, and because there is clear evidence of environmental factors (such as stress) playing a prominent role in its pathogenesis, other groups have postulated that epigenetic findings might be important in FM (Ciampi de Andrade et al., 2017). This is a promising area that needs further research.

2.4 | Qst evidence of cns disturbances in pain and sensory processing

The physiological hallmark and defining feature of central sensitization is altered CNS pain processing. This was originally identified clinically in conditions such as FM and TMD by identifying tenderness to palpation. Following these early clinical observations, many groups have used much more sophisticated QST methods to identify and characterize pain and sensory mechanisms in individuals suspected to have central sensitization (Arendt-Nielsen, 2015; Arendt-Nielsen & Yarnitsky, 2009; Backonja et al., 2013; Cruz-Almeida & Fillingim, 2014; Edwards, Sarlani, Wesselmann, & Fillingim, 2005; Greenspan et al., 2013; Pfau, Geber, Birklein, & Treede, 2012; Wylde et al., 2017). QST refers to procedures in which quantifiable stimuli (e.g., mechanical, thermal, or electric) are delivered in

a systematic manner to the body. An individual's reaction to these stimuli, including nonverbal behavioral responses, such as withdrawal, ratings of perceived stimulus intensity and unpleasantness, and physiological responses, are used to measure sensory gain or loss. Data from QST studies suggest a wide, bell-shaped distribution in pain sensitivity across the general population. Most, but not all, individuals with COPCs, and a subset of individuals with any other chronic pain condition, will typically fall on the right side of the curve, with significant diffuse hypersensitivity outside the region of injury (i.e., secondary hyperalgesia and allodynia) (Ablin & Clauw, 2009; Diatchenko et al., 2006; Fillingim, 2005; Gwilym et al., 2009; Kleinbohl et al., 1999; Neddermeyer, Fluhr, & Lotsch, 2008; Nielsen, Staud, & Price, 2009; Tracey & Bushnell, 2009; Williams & Clauw, 2009). Importantly, this hypersensitivity can be present in both painful/symptomatic, as well as pain-free/nonsymptomatic body sites, which strongly suggests a central pain mechanism. Some of the chronic pain conditions where widespread hyperalgesia/allodynia is consistently identified include FM, IBS, TMD, low back pain, tension headache, chronic pelvic pain, and vulvodynia (As-Sanie et al., 2013; Clauw & Chrousos, 1997; Gibson et al., 1994; Giesecke et al., 2004; Greenspan et al., 2011; Grinberg, Granot, Lowenstein, Abramov, & Weissman-Fogel, 2017; Leffler, Hansson, & Kosek, 2002; Petzke, Harris, Williams, Clauw, & Gracely, 2005; Whitehead et al., 1990; O. H. G. Wilder-Smith, Tassonyi, & Arendt-Nielsen, 2002).

The efficiency of endogenous pain modulation networks is another marker of altered CNS pain processing measured by QST. Endogenous pain inhibitory networks can be activated in humans and animals during application of a noxious "conditioning" stimulus, resulting in attenuation of pain produced by a noxious "test" stimulus applied to a different body location—an effect termed *conditioned pain modulation* (CPM). Although deficient CPM (i.e., reduced inhibition of test stimulus evoked pain) or even facilitation of test stimulus pain has been observed in a subset of healthy individuals (Potvin & Marchand, 2016; Schoen et al., 2016), it is more common in individuals with FM and other COPCs (Granot et al., 2008; Julien, Goffaux, Arsenault, & Marchand, 2005; Kosek & Ordeberg, 2000; Le Bars, Dickenson, & Besson, 1979; Mahomedy, Downing, Jeal, & Coleman, 1976; Nir & Yarnitsky, 2015; Wilder-Smith & Robert-Yap, 2007; Yarnitsky et al., 2008). In fact, a 2012 meta-analysis confirmed that CPM is attenuated in the majority of chronic pain conditions (Lewis, Rice, & McNair, 2012). Decreased CPM is associated with a variety of clinical outcomes, including increased postsurgical pain and analgesia requirements, and the effectiveness of some centrally acting analgesics (Edwards, 2005; Yarnitsky, 2015; Yarnitsky, Granot, Nahman-Averbuch, Khamaisi, & Granovsky, 2012; Yarnitsky et al., 2008). Functional neuroimaging studies have begun to reveal a network of cortical and brainstem regions involved in the normal CPM response in humans (Bogdanov et al., 2015; Piche, Arsenault, & Rainville, 2009; Sprenger, Bingel, & Buchel, 2011; Youssef, Macefield, & Henderson, 2016a,b) that is consistent with earlier studies of endogenous analgesia in animals, and recently we identified an aberrant pattern of PAG-to-brainstem connectivity that may play a role in deficient CPM, or enhanced descending facilitation, in central sensitization (Harper, Ichesco, Schrepf, Hampson, et al., 2018).

Although CPM methods probe for the absence or impairment of inhibitory mechanisms, *temporal summation* of pain measures the amplification of nociceptive signaling related to central sensitization. Experimentally, *temporal summation* refers to an increase in the perceived intensity of pain in response to sequential stimuli of equal physical strength. This response is thought to reflect the progressive increase in neuronal firing of dorsal horn neurons in response to repetitive C-fiber stimulation (i.e., windup) (Graven-Nielsen et al., 2000; Price, Mao, Frenk, & Mayer, 1994; Price et al., 2002; Staud, Vierck, Cannon, Mauderli, & Price, 2001; Weissman-Fogel et al., 2009); however, supraspinal mechanisms contribute to the regulation of this phenomenon (Cheng, Erpelding, Kucyi, DeSouza, & Davis, 2015). Temporal summation is a normal response that occurs in healthy humans, but is enhanced in patients with central sensitization, and has been shown to predict pain outcomes (Arendt-Nielsen et al., 2010; Maixner, Fillingim, Sigurdsson, Kincaid, & Silva, 1998; Sarlani, Grace, Reynolds, & Greenspan, 2004; Staud, Craggs, Perlstein, Robinson, & Price, 2008; Weissman-Fogel et al., 2009). For example, patients with osteoarthritis that report chronic pain after joint replacement surgery have significantly higher temporal summation preoperatively and postoperatively, compared to patients that experience pain relief (Izumi, Petersen, Laursen, Arendt-Nielsen, & Graven-Nielsen, 2017; Petersen, Arendt-Nielsen, Simonsen, Wilder-Smith, & Laursen, 2015; Skou et al., 2013).

This suggests that enhanced temporal summation may be a marker for vulnerable individuals with central sensitization that respond poorly to peripherally directed pain interventions. CPM and temporal summation paradigms can also be used in combination to better characterize the balance of pro- and antinociceptive processing within individuals (Petersen, Graven-Nielsen, Simonsen, Laursen, & Arendt-Nielsen, 2016; Vaegter & Graven-Nielsen, 2016; Yarnitsky, Granot, & Granovsky, 2014). Additional QST measures that may show altered endogenous pain modulation in patients with central sensitization include assessments of pain after-sensations (pain sensations that linger after cessation of painful stimulation, Staud, Koo, Robinson, & Price, 2007), and offset analgesia (a disproportionate reduction in perceived pain following a subtle decrease in the intensity of painful stimulation; Hermans et al., 2016; Oudejans, Smit, van Velzen, Dahan, & Niesters, 2015).

In addition to hypersensitivity to painful stimuli, there is accumulating evidence that many patients with central sensitization exhibit hypersensitivity to nonpainful stimuli that bypass peripheral and spinal pathways. Patients with FM demonstrate perceptual amplification of auditory stimuli, and rate everyday sounds as more unpleasant compared to controls (Carrillo-de-la-Pena, Vallet, Perez, & Gomez-Perretta, 2006; Dohrenbusch, Sodhi, Lamprecht, & Genth, 1997; Geisser, Glass, et al., 2008; McDermid, Rollman, & McCain, 1996; Wilbarger & Cook, 2011). Similar findings have been observed in TMD (Hollins et al., 2009), rheumatoid arthritis (McDermid et al., 1996), and IBS (Berman et al., 2002; Blomhoff, Jacobsen, Spetalen, Dahm, & Malt, 2000). FM patients have also been shown to have increased sensitivity to complex visual stress (Harte et al., 2016), light (Martenson et al., 2016), and unpleasant odors (Schweinhardt, Sauro, & Bushnell, 2008). These findings, coupled with evidence that auditory and visual sensitivities are often correlated with pain sensitivity in these patients (Schrepf, Williams, Gallop et al., 2018; Geisser, Glass et al., 2008; Harte et al., 2016), have led us and others to hypothesize that a generalized or global state of CNS sensory amplification may play a role in the pathogenesis of chronic pain disorders, and that these sensory measures may mark an important individual patient endophenotype of central sensitization (Schrepf, et al., 2018; Geisser, Donnell, et al., 2008; Hollins et al., 2009; McDermid et al., 1996). *In fact, we propose that this might be one fundamental neurobiological difference between chronic pain patients with "top-down" central pain mechanisms, where increased sensitivity to a range of painful and nonpainful sensory stimuli is present, and those with "bottom-up" central pain mechanisms, traditionally referred to as central sensitization, where only pain processing might be augmented.* This is supported by the fact that functional imaging studies find that the insula, a brain region that also plays a role in multisensory integration, is hyperactive in most individuals with central sensitization (Brooks & Tracey, 2007; Wager et al., 2013).

2.5 | Brain imaging studies

The observation that QST outcomes in individuals with FM showed diffuse tenderness has led to subsequent brain neuroimaging studies that have been among the best "objective" evidence that the pain in FM and related pain syndromes are "real," and that the brain is playing a prominent role in pain pathophysiology (Harris & Clauw, 2006).

Early studies demonstrated increased neuronal activity in CNS sensory-processing regions in patients with central sensitization exposed to sensory stimuli that healthy individuals find innocuous (Cook et al., 2004; Gracely, Petzke, Wolf, & Clauw, 2002; Gracely et al., 2004; Hampson et al., 2013; Naliboff et al., 2001). More recent neuroimaging studies provide further insight into the underlying CNS changes in central sensitization, and demonstrate significant structural, chemical, and functional alterations in pain-related brain areas. As a broad overview, changes in brain gray matter are noted in pain-processing regions such as: the thalamus; periaqueductal gray (PAG); insula; cingulate and somatosensory cortices (Smallwood et al., 2013); neurochemical alterations, including increased levels of excitatory neurotransmitters (e.g., glutamate) and decreased levels of inhibitory neurotransmitters (e.g., γ-aminobutyric acid [GABA] are present in the insula (Harris & Clauw, 2012); and increased resting

brain network connectivity to pronociceptive brain areas; and decreased connectivity to antinociceptive brain areas are also often present in central sensitization (Ichesco et al., 2014; Jensen et al., 2009; Loggia et al., 2013; Napadow, Kim, Clauw, & Harris, 2012). As such, multiple brain neuroimaging studies have found alterations in supraspinal pain processing in individuals with clinical features suggestive of central sensitization.

Functional magnetic resonance imaging (fMRI), in conjunction with QST, has been used to further demonstrate that patients with central sensitization exhibit a supraspinal-mediated multisensory hypersensitivity. We recently found that the insula was activated by an aversive visual stimulus, and that the degree of activation was strongly associated with patients' self-reported FM pain (Harte et al., 2016). Moreover, this activity within the insula was reduced following administration of pregabalin (but not placebo), and the analgesic effectiveness of this drug was associated with a concomitant reduction in the insula's response to the visual stimulus. In addition to sensitivity to visual stimuli, methods such as fMRI clearly demonstrate that individuals with FM display increased brain activity when given a mild pressure or heat stimulus that most individuals would feel as "touch" or "warmth," rather than "pain." During this experience of pain, similar brain activation patterns arise in the patients that are typically seen in pain-processing regions that normal pain-free individuals experience during a noxious stimulus (Cook et al., 2004; Gracely, Petzke, Wolf, & Clauw, 2002). This indicates that individuals with central sensitization have a similar brain response to painful stimuli as controls, but at lower levels of stimulus intensity.

A more recent advance in fMRI research is to examine the extent that brain regions are "connected" to each other (i.e., simultaneously activated [or deactivated] (Ploner, Lee, Wiech, Bingel, & Tracey, 2010), simply at rest. The advantage of these types of resting-state analyses is that they provide a window into brain changes associated with chronic, ongoing spontaneous pain. Individuals with FM have increased connectivity between the insula and neural networks not normally thought to be involved with pain, such as the *Default Mode Network* (DMN), and the degree of this hyperconnectedness is related to the severity of ongoing pain (Napadow et al., 2010, 2012). A different group has shown that, during a painful stimulus, connectivity is decreased between key antinociceptive regions (e.g., the brainstem—the origin of descending analgesic pathways) and a region they previously identified to be a potential source of dysfunctional pain inhibition in FM (Jensen et al., 2009; Jensen et al., 2012). Similar to the studies of visual stimulation described above, Lopez-Sola and colleagues demonstrated that individuals with central sensitization are more sensitive to a number of nonpainful sensory stimuli, and that machine-learning paradigms can accurately distinguish FM from non-FM patients with over 90% accuracy using fMRI results (Lopez-Sola et al., 2014, 2017).

Other neuroimaging techniques have been used to identify neurotransmitter and receptor abnormalities that may be driving the pain amplification seen in FM and other central sensitization pain disorders. Wood and colleagues used positron emission tomography (PET) to show that attenuated dopaminergic activity may be playing a role in pain transmission in FM, and we showed evidence of decreased *mu* opioid receptor availability (possibly due to an increased release of endogenous *mu* opioids) in FM (Harris et al., 2007; Wood et al., 2007). Recent work by Schrepf and colleagues used multimodal fMRI-PET to demonstrate that this reduction in opioid receptor-binding is related to reduced antinociceptive brain responses in the anterior cingulate cortex—providing further support for a potential endogenous opioid mechanism in pain central sensitization (Schrepf et al., 2016). This latter finding, as well as previous studies showing increased levels of endogenous opioids in the cerebrospinal fluid (CSF) of FM patients (Baraniuk, Whalen, Cunningham, & Clauw, 2004), have been suggested as evidence of why opioid analgesics appear to have poor efficacy in FM.

Our group and others have used proton spectroscopy (^{1}H-MRS) to probe other neurotransmitters, including glutamate and GABA. These studies have shown increases in brain concentrations of glutamate in pain-processing regions, such as the insula in FM (Harris, 2010; Harris et al., 2009; Harte, Clauw, Napadow, & Harris, 2013; Pyke, Osmotherly, & Baines, 2017). This finding has also been noted in the CFS of FM patients (Sarchielli, Di Filippo, Nardi, & Calabresi, 2007). Drugs that improve FM pain, such as pregabalin and gabapentin, are hypothesized to be working in part by reducing glutamatergic activity in the brain (Maneuf, Hughes, & McKnight, 2001). In support of this, we demonstrated that baseline glutamate levels and functional connectivity of the insula predicted which FM patients would successfully respond to pregabalin therapy (Harris et al., 2013). Patients with higher posterior

insular glutamate and insular connectivity to the DMN had the most improvement in pain and hyperalgesia following pregabalin. Furthermore, improvement in pain was accompanied by normalization of the glutamate and functional connectivity findings, demonstrating that these abnormalities were at least partly responsible for pain pathogenesis (Harris et al., 2013). We have similarly shown that *decreased connectivity to antinociceptive* brain regions, such as the periaqueductal gray (PAG—a critical locus of descending analgesic pathways), predicts responsiveness to milnacipran, a serotonin norepinephrine reuptake inhibitor (Schmidt-Wilcke et al., 2014).

Conversely, ^{1}H-MRS has been used to demonstrate low levels of one of the body's major inhibitory neurotransmitters (GABA; Foerster et al., 2012; Harper, Ichesco, Schrepf, Halvorson, et al., 2018), and this likely accounts for the efficacy of medications such as gamma-hydroxybutyrate in FM (Russell et al., 2011). This finding may also suggest biological plausibility for the association between low–moderate alcohol consumption (compared to none or heavy drinking), and improved symptomatology and functionality in FM (Kim et al., 2013; Scott et al., 2018). Alcohol enhances inhibitory GABAergic neurotransmission (Chandler, Overton, Ruedi-Bettschen, & Platt, 2017; Chastain, 2006) and may exhibit a U-shaped curve for its analgesic effects similar to its potentially beneficial cardiovascular effects. That imbalances between excitatory and inhibitory neurotransmitters are not found diffusely throughout the brain and, instead, appear to be localized to regions that contribute to multisensory processing (e.g., insula) (Brooks & Tracey, 2007; Craig, 2002), is consistent with the notion that a global sensory hyper-responsiveness is partly responsible for the pathophysiology of FM and related COPCs (Ablin & Clauw, 2009; Yunus, 2007). Figure 1 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 analgesic is likely to work in every patient with pain of CNS origin.

Functional magnetic resonance imaging has also proven useful in determining how comorbid psychosocial factors influence pain processing in FM. For example, in FM patients with variable degrees of comorbid depression, anterior insula and amygdala activations were correlated with depressive symptoms, consistent with these "medial" and prefrontal brain regions being involved with affective or motivational aspects of pain processing (and being more closely related to unpleasantness, rather than the sensory intensity of pain) (Berna et al., 2010). However,

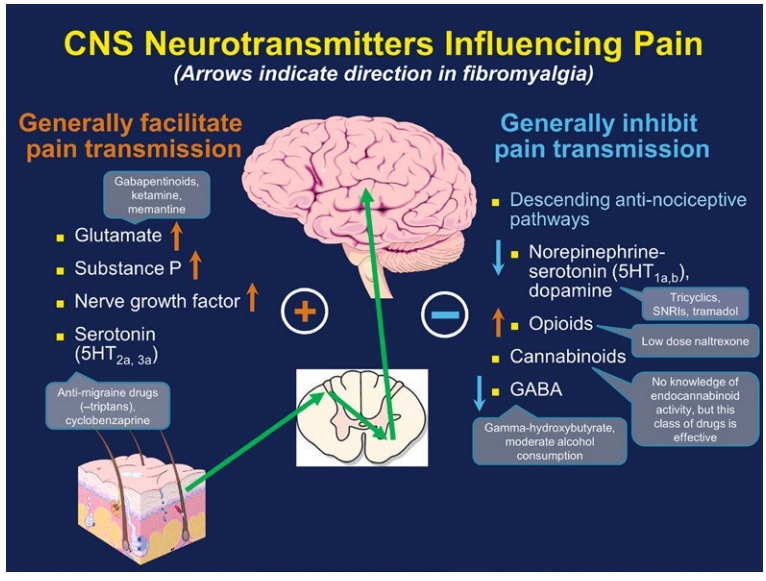


FIGURE 1 Neurotransmitter systems that generally facilitate (left side) or inhibit (right side) central nervous system (CNS) pain transmission. The arrows indicate the levels of these neurotransmitters in the CNS of individuals with fibromyalgia (FM), and the boxes indicate drugs that have been shown to be effective in FM that are likely working in part via those neurotransmitters (Clauw, 2014; Schmidt-Wilcke & Clauw, 2011)

the degree of neuronal activation in more lateral structures generally thought to be associated with the sensory-processing of pain (i.e., location and intensity of the pain) were not associated with levels of depressive symptoms, or the presence or absence of major depression. This is consistent with substantial evidence that pain and depression are largely independent, but overlapping, physiological processes.

2.6 | The role of neuroendocrine or autonomic abnormalities

Because of the link between COPCs and exposure to stress, and because both the neuroendocrine and autonomic nervous systems could cause many of the symptoms of these conditions, these factors have been fairly extensively studied, especially in FM and CFS (Clauw & Crofford, 2003; Crofford, 1998; Demitrack & Crofford, 1998). However, this research has generally yielded inconsistent findings, and treatment studies targeting these systems have failed (Adler, Kinsley, Hurwitz, Mossey, & Goldenberg, 1999; Cohen et al., 2000; Crofford et al., 1994; Demitrack & Crofford, 1998; Martinez-Lavin, Hermosillo, Rosas, & Soto, 1998; Qiao, Vaeroy, & Morkrid, 1991). These studies note either hypo- or hyperactivity of both the hypothalamic pituitary adrenal axis (HPA) and sympathetic nervous system in individuals with FM and related conditions, and the precise abnormality varies from study to study. Moreover, these studies only find "abnormal" HPA or autonomic function in a very small percentage of patients, and there is tremendous overlap between cases and controls in many of these studies. Taken together, these factors are now generally thought to play some role in a subset of individuals, but not in all individuals with these conditions.

The inconsistency of these findings may be explained by the fact that nearly all of these studies were cross-sectional and assumed that, if HPA and/or autonomic dysfunction was found in these conditions, it must have *caused* the pain and other symptoms. Data now suggest the opposite. As noted above, more convincing data suggest that these factors (especially HPA abnormalities) might represent a *diathesis* or be *due to* pain or early life stress, rather than causing it. Notably, in two studies examining HPA function in FM, McLean and colleagues showed that salivary cortisol levels covaried with pain levels, and that CSF levels of corticotropin-releasing factor (CRH) were more closely related to an individual's pain level or a history of early life trauma than whether they were a FM patient or control (McLean et al., 2005, 2006). Because most previous studies of HPA and autonomic function in FM failed to control for pain levels, a previous history of trauma, or other comorbid disorders that could affect HPA or autonomic dysfunction, these inconsistencies are not surprising.

2.7 | Evidence of abnormal cytokines and immune dysfunction in central sensitization

Although the prevailing view is that FM and related COPCs are not autoimmune disorders, and that classic anti-inflammatory agents are not of benefit in these conditions, there are some data suggesting that the immune system may be playing a role in their pathogenesis (Gur & Oktayoglu, 2008). Perhaps the most consistent finding noted to date is a mild elevation in IL-8, which is a cytokine associated with sympathetic function (Bazzichi et al., 2007; Wallace, Bowman, Wormsley, & Peter, 1989). In other conditions closely linked to FM, such as interstitial cystitis, more sensitive assays of immune system function, that can be gleaned by stimulating peripheral immune cells, have been shown to be abnormal (Schrepf et al., 2015). We and others have speculated that diet or obesity could contribute to this low-grade inflammation in FM, and might be a potential target for therapy (Schrepf et al., 2017); while others have posited that this may provide evidence of microglia involvement in FM. These areas warrant further exploration, and are actively being investigated.

2.8 | The role of "small fiber neuropathy" in central sensitization

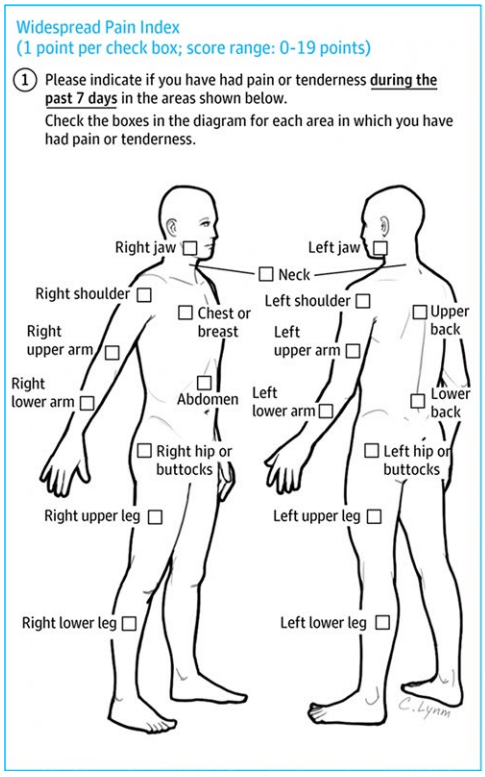
Many groups have now shown evidence of decreased intraepidermal nerve fiber density (i.e., small fiber neuropathy) in FM (Caro & Winter, 2015; Doppler, Rittner, Deckart, & Sommer, 2015; Kim, Kim, Oh, & Clauw, 2008; Levine

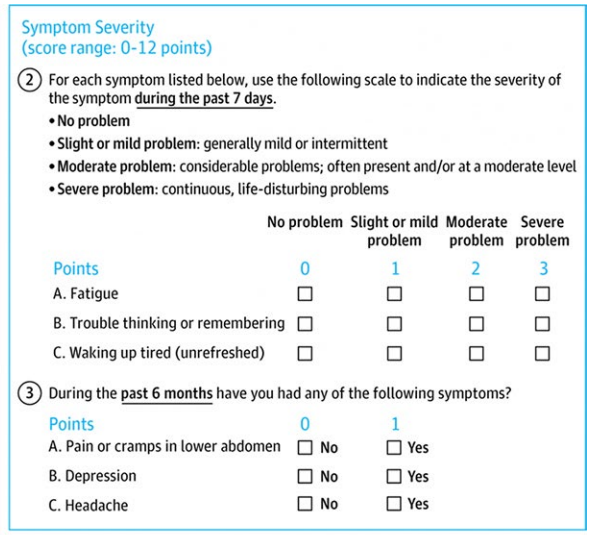
& Saperstein, 2015; Oaklander, Herzog, Downs, & Klein, 2013; Uceyler et al., 2013). However, debate remains regarding the meaning of these findings (Clauw, 2015). Reduced nerve fiber density is a very nonspecific finding that has now been noted in over 50 different pain and nonpain conditions (Clauw, 2015). Moreover, Harte and colleagues recently demonstrated that these findings could be induced in an animal model of central sensitization by increasing insular glutamate (Harte et al., 2017). We believe that this nonspecific finding reflects an adaptive structural and functional reorganization of the peripheral nervous system, not unlike the changes in the CNS noted via voxel-based morphometry of the brain in chronic pain states (Smallwood et al., 2013), in the context of ongoing chronic pain and other neurological conditions. The hyperexcitable C nociceptors noted in FM by Serra and colleagues could also be secondary to CNS disinhibition of peripheral systems, rather than indicating that there is primary pathology in the periphery (Serra et al., 2014). Regardless, the current evidence does not merit routine skin biopsies in suspected FM patients, and certainly does not yet suggest that this finding is of enough pathophysiological significance to support the (noninvestigational) use of aggressive cytotoxic and anti-inflammatory regimens that some have proposed. When considering the available data regarding the pathophysiology of FM, including the brain neuroimaging and multisensory hypersensitivity findings discussed above, the data strongly favor CNS factors rather than peripheral abnormalities, and these findings should continue to drive clinical care.

3 | THE CONCEPT OF CENTRAL SENSITIZATION AS A CONTINUUM—RATHER THAN PRESENT OR ABSENT

Wolfe was the first to describe the concept of "fibromyalgianess," by showing the importance of "subsyndromic" or "subthreshold" FM (Wolfe, 2009). In a series of studies, he showed that, in individuals with conditions such as rheumatoid arthritis, low back pain or osteoarthritis, an individual's FM score, derived with measures very similar to the 2010/11/16 American College of Rheumatology (ACR) FM criteria (Wolfe, Clauw, et al., 2010; Wolfe et al., 2011; Wolfe et al., 2016), was typically more predictive of pain and disability than more objective measures of activity of these illnesses, such as measures of inflammation or joint damage (Wolfe, Michaud, Li, & Katz, 2010; Wolfe et al., 2014). The survey version of these criteria, designed for clinical and epidemiological research, is entirely patient self-report, and can be administered on a single piece of paper (Wolfe et al., 2011). Our group uses the *Michigan Body Map* (Brummett, Bakshi et al., 2016) to assess the *Widespread Pain Index* (up to 19 body areas each counted as 1 point), as well as the *Symptom Severity Index* that queries 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; Figure 2). The *Widespread Pain Index* and *Symptom Severity Index* are combined for a total FM score of 0–31. When employed as a dichotomous measure with a variety of "cut points" that can be used, this measure will roughly identify most of the same individuals as the original tender point-based 1990 FM criteria (except with many more males) (Wolfe, Clauw, et al., 2010; Wolfe et al., 2011). However, when FM is considered more as a physiological construct to determine where on the continuum of central sensitization an individual is, then this score can be used as a continuous measure (i.e., reflecting the degree of *fibromyalgianess* or central sensitization) that can be useful in the diagnosis and treatment of virtually any patient with a rheumatic disorder who is experiencing pain (Wolfe, 2009).

The FM score was recently shown to be associated with diffuse hyperalgesia on QST in females with knee osteoarthritis (Neville et al., 2018), and an index of widespread pain was used to identify aberrant brain structure and connectivity in pelvic pain patients with interstitial cystitis that was indistinguishable from women with FM (Kutch et al., 2017). Furthermore, a recent fMRI study by Basu and colleagues has shown that perhaps the most consistently found feature of central sensitization in COPCs—increased connectivity between the DMN and the insula—was also found to correlate strongly with the degree of FM that is present in individuals with rheumatoid arthritis (Basu et al., 2018). Importantly, these data support the notion that central sensitization pathology exists





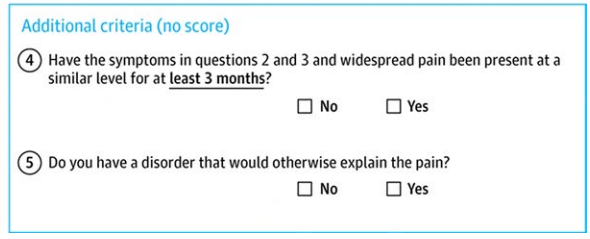


FIGURE 2 The 2011 Survey Criteria for Fibromyalgia (Wolfe et al., 2011) using the Michigan Body Map (Brummett, Bakshi et al., 2016)

in non-FM pain states, and that tools such as the FM survey criteria provide a useful self-report measure of this construct.

In several recent studies, this concept of *fibromyalgianess* or subsyndromal FM has been shown to be very clinically important. In these studies by Brummett and colleagues, individuals who were scheduled for either lower extremity joint replacement or hysterectomy completed a broad-battery of validated self-report measures prior to their surgery. It was hypothesized that higher FM scores on the 2011 FM survey criteria (Wolfe et al., 2011) would predict increased opioid requirements in the inpatient admission following surgery, as well as long-term postsurgical pain outcomes. Again, this measure is scored from 0 to 31, with a score of 13 typically used as the diagnostic cut-off point for FM. These studies demonstrated that, for each 1-point increase in this measure from 0 to 31, individuals needed an adjusted 7–9 mg more oral morphine equivalents to control their pain in the first 24–48 hr following surgery, and were 15%–20% less likely to show pain improvement following surgery (Brummett et al., 2013, 2015; Janda et al., 2015). These findings were independent of a number of preoperative characteristics, including age, sex, anxiety, depression, catastrophizing, and opioid use. More importantly, these findings were linear, and the same incremental increase in opioid requirements and surgery nonresponsiveness was observed both in individuals well below the threshold to diagnose FM, and in individuals exceeding this threshold. Figure 3 shows two different individuals with osteoarthritis, neither of whom would meet criteria for FM, but who are at different points along the *fibromyalgianess* continuum, and shows the marked difference in opioid responsiveness and improvement in pain following arthroplasty that these two individuals would experience. These data suggest that the degree of central sensitization reflected in this measure may help identify individuals in perioperative or other settings who are less likely to respond to peripherally directed treatments such as surgery.

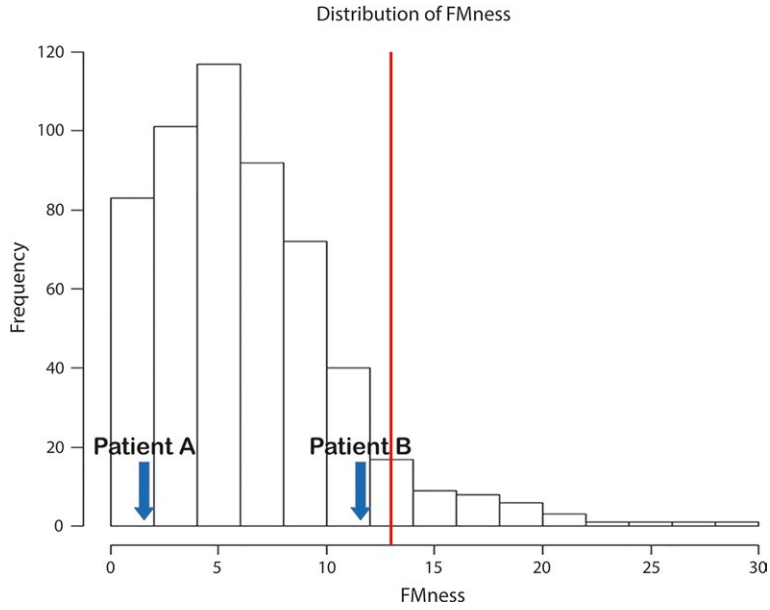


FIGURE 3 Fibromyalgianess (FMness) scores from individuals undergoing lower extremity arthroplasty for osteoarthritis (Brummett et al., 2013; Brummett et al., 2015). The red line indicates the score that is used to classify an individual as being FM positive. Two different hypothetical participants, who do not meet criteria for FM, are compared with respect to the amount of opioids (in oral morphine equivalents, OME) required for pain control during a 24-48-hour inpatient period and the likelihood of achieving 50% improvement in pain at six months following surgery. Compared to Patient A with localized pain and no somatic symptoms, Patient B would need 90 mg more OME during the first 48 hours of hospitalization, and would be five times less likely to have a 50% improvement in pain at six months.

4 | SUMMARY AND CONCLUSION

As the use of the term central sensitization has expanded over the past several decades, so has our understanding of CNS processes that may lead to this phenomenon. Initially thought to be confined to the spinal cord, supraspinal mechanisms are now understood to play a significant role in many individuals who have this phenomenon. One demarcation that is becoming increasingly clear, but has received little attention in the pain field, is how to differentiate whether an individual with this process has a problem that is being driven by ongoing nociceptive input (i.e., the original use of the term), or whether this process is occurring in the absence of a peripheral driver (as seems to be occurring in many individuals with COPCs). Figure 4 denotes these two subtypes of central sensitization as *bottom-up* (i.e., being driven by ongoing nociceptive input, and presumably found in individuals with autoimmune disorders, sickle cell disease, hypermobility syndromes), or *top-down* (i.e., where the primary problem may very well likely originate in supraspinal structures and does not require ongoing nociceptive input to maintain the process). This figure reviews what we now know about these two subtypes, but this is an area that requires much more investigation. The clinical reason for differentiating these two subtypes of altered CNS processing of pain should be obvious—the *bottom-up* form should be treated aggressively with interventions aimed at reducing peripheral nociceptive drive, whereas CNS-directed therapies will be necessary for the *top-down* form. As our understanding of these two subtypes evolves, so should our sematic terms, and these authors suggest that the term central sensitization is only used to denote the *bottom-up* form, and a new term (e.g., *central hypersensitivity*) be used to denote the *top-down* form. We further propose that, taken together, both forms constitute a broader clinical construct of "centralized pain" that exists as a continuum across individuals with chronic pain. Many individuals with centralized pain are likely to have combinations of these two processes, and will need to be treated with both peripherally- and centrally-directed therapies.

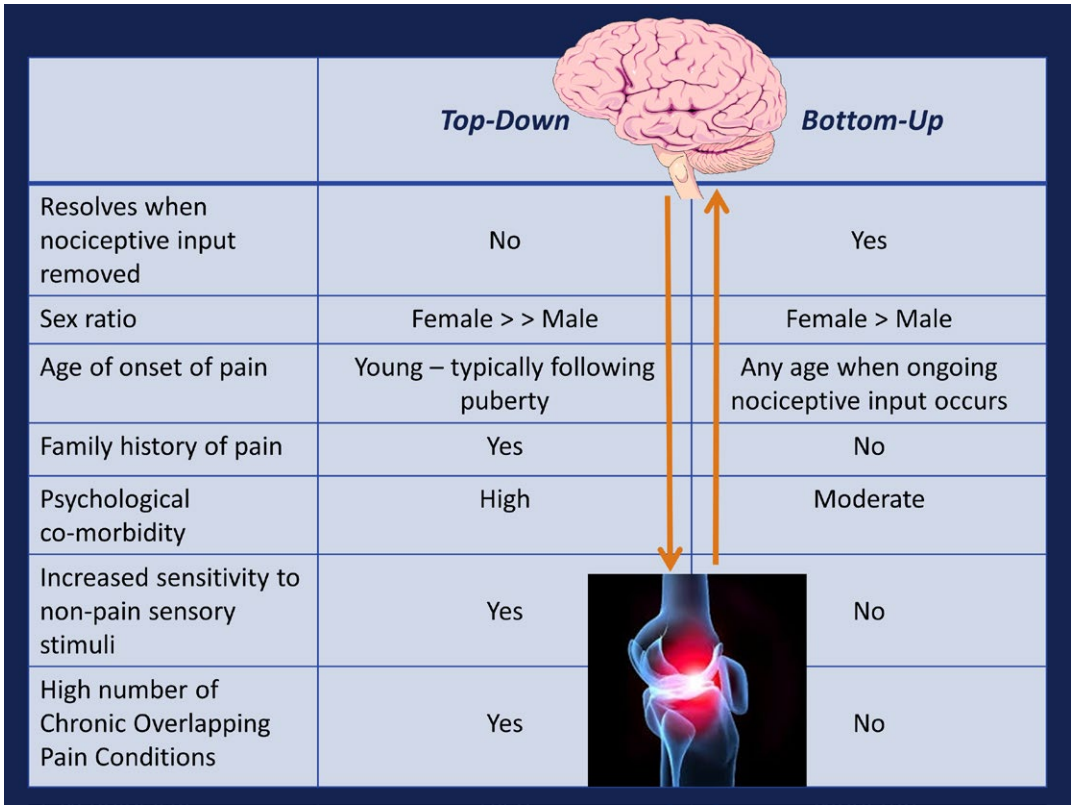


FIGURE 4 Differences between "top-down" and "bottom-up" forms of central sensitization

DISCLOSURES

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