Published in final edited form as:
Pain Manag Nurs. 2011 March ; 12(1): 15–24. doi:10.1016/j.pmn.2009.10.003.

Central Sensitivity Syndromes: Mounting Pathophysiologic Evidence to Link Fibromyalgia with other Common Chronic Pain Disorders

Lindsay L. Kindler, PhD, RN[1], **Robert M. Bennett, MD**[2,3], and **Kim D. Jones, PhD, RN, FNP**[2,3]

[1]University of Florida, Center for Comprehensive Pain Research

[2]Oregon Health & Science University, School of Nursing

[3]Oregon Health & Science University, School of Medicine

Abstract

Objective—To review emerging data from the fields of nursing, rheumatology, dentistry, gastroenterology, gynecology, neurology, and orthopedics that supports or disputes pathophysiologic similarities in pain syndromes studied by each specialty.

Methods—A literature search was performed through PubMed and Ovid using the terms fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, irritable bladder/ interstitial cystitis, headache, chronic low back pain, chronic neck pain, functional syndromes and somatization. Each term was linked with pathophysiology and/or central sensitization. This paper presents a review of relevant articles with a specific goal of identifying pathophysiological findings related to nociceptive processing.

Results—The extant literature presents considerable overlap in the pathophysiology of these diagnoses. Given the psychosomatic lens through which many of these disorders are viewed, demonstration of evidence based links supporting shared pathophysiology between these disorders could provide direction to clinicians and researchers working to treat these diagnoses.

Conclusions—Central sensitivity syndromes denotes an emerging nomenclature that could be embraced by researchers investigating each of these disorders. Moreover, a shared paradigm would be useful in promoting cross-fertilization between researchers. Scientists and clinicians could most effectively forward the understanding and treatment of fibromyalgia and other common chronic pain disorders through an appreciation of their shared pathophysiology.

Keywords

Central sensitization; fibromyalgia; pain processing; hyperalgesia

Corresponding author: Lindsay L. Kindler, PhD, RN, Postdoctoral fellow, Comprehensive Center for Pain Research, University of Florida, 1600 SW Archer Road, Room D2–13, PO Box 10044, Gainesville, FL 32610-0444, 503-680-7484, lkindler@dental.ufl.edu.

Introduction

Contemporary research into the mechanisms of pain in fibromyalgia (FM) has identified this syndrome as a disorder of nociceptive processing. Fibromyalgia is characterized by chronic widespread pain (CWP) as defined by pain in three out of four body quadrants and pain on palpation of at least eleven out of eighteen specified tender points (Wolfe, et al., 1990). While centrally mediated augmentation of pain in FM results in widespread hypersensitivity, mounting evidence suggests that similar pathophysiological processes result in hyperalgesia outside the apparent anatomical focus of pain in regional pain syndromes such as tempromandibular disorder (TMD), irritable bowel syndrome (IBS), interstitial cystitis (IC), headache, chronic low back pain, and chronic neck pain. Recent investigations reveal that these pain disorders are linked by a unifying pathological process of dysregulated nociception, referred to as “central sensitization”. In addition to shared mechanisms of pain, these disorders often co-occur (Aggarwal, McBeth, Zakrzewska, Lunt, & Macfarlane, 2006), may act as risk factors for the development of one another (Diatchenko, Nackley, Slade, Fillingim, & Maixner, 2006), or lead to the transition from a localized pain disorder to a widespread pain disorder (Holm, Carroll, Cassidy, Skillgate, & Ahlbom, 2007; Lapossy, Maleitzke, Hrycaj, Mennet, & Muller, 1995; Macfarlane, 1999). While the initiation of several of these disorders comes from peripheral pain producing mechanisms (inflammation and/or mucosal or neural irritation), persistent nociceptive input leads to changes in the central nociceptive system. Following the induction of central sensitization, painful sensations can arise independent of peripheral nociceptive input (Latremoliere & Woolf, 2009), significantly increasing the complexity of treating these disorders. Expanding our understanding of the shared pathophysiology among these disorders will promote collaboration among researchers from different disciplines to gain insight into the underlying mechanisms and promote treatment of these disorders of pain processing. The goal of this paper is to outline the pathophysiological processes shared by these chronically painful conditions.

Methods

A literature search was performed through Pubmed and Ovid using the following search terms: fibromyalgia, tempromandibular disorder, irritable bowel syndrome, irritable bladder syndrome, interstitial cystitis, headache, chronic low back pain, and chronic neck pain. Each term was then linked to the terms pathophysiology and/or central sensitization. Eight hundred and forty nine relevant articles were reviewed with a specific goal of identifying pathophysiological findings related to nociceptive processing. One hundred and seventy six articles were original research and 48 were major reviews or consensus statements. The bibliographies of these articles as well as unpublished peer reviewed abstracts from major relevant scientific proceedings were also evaluated. Ultimately 78 articles were chosen based on pre-determined methodological criteria such as research with a theoretical framework based on known pathophysiological mechanisms, inclusion of subjects who met specialty specific diagnostic criteria but were free of confounding comorbidities and use of valid and reliable psychophysical testing modalities. Scientific reviews that addressed central sensitization in chronic pain disorders and utilized similar methodological criteria were also included.

Pathophysiology

The notion that persistent pain may lead to neuroplastic changes within the peripheral and central nervous system is now firmly established. The following outlines the general principles of pain neuroplasticity. It was originally observed, in animals, that repetitive C fiber stimulation exponentially increases dorsal horn stimulation, such that the same level of

stimuli produces a progressive increase in activation of second order neurons projecting to the brain (Mendell, 1966; Yunus, 2008). This phenomenon, termed “wind up”, represents one major mechanism through which ongoing pain produces a hyperexcitable state within the central nervous system. It is now understood that pain impulses originating in peripheral nerve endings (“nociceptors”) activate both A delta and C nociceptive fibers. These are the nerve fibers that carry the nociceptive impulse to dorsal horn neurons in the spinal cord. Some of these neurons are multi-modal, and respond to the sensations of touch, pressure, temperature and pain, and are thus called wide dynamic range neurons. Chronic pain causes a persistent activation of A delta and C fibers, stimulating the release of neurotransmitters and neuromodulators (i.e. substance P, nerve growth factor, calcitonin gene related peptide, glutamate, and aspartate) into the dorsal horn synapse (Urban & Gebhart, 1999). Influx of these neurochemicals sensitizes the WDR neurons such that they become hyperexcitable, responding to lower levels of nociceptive stimuli (i.e. hyperalgesia) as well as some previously non-painful stimuli (i.e. allodynia) (Eide, 2000). Expansion of receptive fields represents another important mechanism through which central sensitization modulates the expression of hyperalgesia. This occurs as a result of prolonged excitation of WDR neurons, which in turn activates adjacent neurons; thus expanding their receptive fields beyond the site of the original injury. Clinically this results in pain being experienced by stimulation of locations that had not previously provoked a pain response (Coderre, Katz, Vaccarino, & Melzack, 1993; Nielsen & Henriksson, 2007).

While our understanding of the development of chronic pain states and hyperalgesia has traditionally focused on transmission of pain through ascending pathways (from the periphery to spinal and supraspinal centers), a growing body of research expands our understanding of descending influences on the generation and maintenance of sensitization (Heinricher, Tavares, Leith, & Lumb, 2009; Tracey & Dunckley, 2004). The periaqueductal gray-rostral ventromedial medulla (PAG-RVM) system is central to the descending modulation of pain. The descending inhibitory (anti-nociceptive) influences of this system have long been reported (Mayer, Wolfle, Akil, Carder, & Liebeskind, 1971). The first evidence came from studies demonstrating that stimulation of the PAG produced profound analgesia in rats (Porreca, Ossipov, & Gebhart, 2002). Further study demonstrated that the PAG-RVM involved stimulation of descending serotonergic, noradrenergic, and opioid pathways that affect an analgesic response at the level of the dorsal horn. Diffuse noxious inhibitory control (DNIC) represents one model in which nociceptive stimuli activates the PAG and RVM producing descending inhibitory control (Marchand, 2008). Diffuse noxious inhibitory control is also described as counter-irritation in which one noxious stimulus inhibits the perception of a second painful stimulus (Campbell, et al., 2008). Stress, attention and expectation can also activate endogenous inhibitory mechanisms as demonstrated in the placebo literature (Benedetti, 2006).

Persuasive evidence suggests that descending pathways can play a facilitatory as well as an inhibitory role (Suzuki, Rygh, & Dickenson, 2004). Descending control through the RVM represents a balance between enhancing and inhibiting nociception and may shift to play a more pro-nociceptive role under certain conditions. There is reasonable evidence that descending facilitation also plays a contributory role in central sensitization and the development of widespread hyperalgesia (Heinricher, et al., 2009). The neurophysiology of this system posits that under prolonged nociceptive input, neurons in the RVM undergo changes in excitability that can in some circumstances serve to maintain central sensitization (Gebhart, 2004). Neurons in the RVM are classified into “ON-cells”, “OFF-cells”, and “NEUTRAL-cells”. ON-cells play a role in descending facilitation whereas OFF-cells correspond to nociceptive inhibition (Porreca, et al., 2002). Although the role of NEUTRAL-cells is less clear, one theory proposes that they are recruited to become either ON or OFF-cells, perhaps playing a role in the shifting balance between RVM inhibition or

facilitation (Heinricher, et al., 2009). A shift in balance where ON-cells become more active is characterized by a decreased nociceptive threshold as descending facilitation predominates. Thus, in the face of persistent nociceptive input, excitatory changes within the neurons of the RVM could produce an imbalance in facilitatory influences that maintain a hyperalgesic state (Porreca, et al., 2002). Therefore ascending alterations characteristic of central sensitization along with the abnormal descending modulation combine to initiate and maintain widespread hyperalgesia.

While FM, TMD, IBS, IC, headache, chronic low back pain and chronic neck pain all display characteristics of central sensitization, pain processing alterations in these disorders could come secondary to ongoing painful input or represent a primary mechanism of the disease (Ness, Powell-Boone, Cannon, Lloyd, & Fillingim, 2005). Whether pain processing abnormalities are secondary to or precede the development of these chronic pain disorders remains an important area of research and could vary by pain processing disorder. Some of these conditions arise from pathological changes in the periphery which lead to centralized changes in nociceptive processing while peripheral instigators are more difficult to identify in other disorders. The following sections will review findings of central sensitization in these conditions.

Fibromyalgia

It has become a generally accepted paradigm that central sensitization and impaired descending pain modulation are two underlying mechanisms causing widespread hypersensitivity to pain in fibromyalgia (FM) (Perrot, Dickenson, & Bennett, 2008; Staud & Rodriguez, 2006). Attributes of FM that support the role of central sensitization include decreased pain thresholds and enhanced sensitivity outside of typical tender point locations, expansion of pain receptive fields, increased levels of substance P and nerve growth factor in the cerebral spinal fluid, abnormal windup, and prolonged pain after cessation of painful input (Dadabhoy, Crofford, Spaeth, Russell, & Clauw, 2008; Giovengo, Russell, & Larson, 1999; Staud & Domingo, 2001). As previously noted, windup describes the changes that occur following ongoing painful input that result in increased excitability of dorsal horn neurons, enhanced responsiveness to painful and non-painful input, and an increase in spontaneous activity (Staud, Price, Robinson, Mauderli, & Vierck, 2004). This phenomenon is a normal occurrence to painful stimuli, but FM patients demonstrate enhanced windup with a greater degree of neuronal excitability and prolonged after sensations (Staud, 2007). This means that wide dynamic range neurons have a lower firing threshold and take longer to resolve following cessation of the stimuli. Research demonstrates that substance P levels in FM patients are two to threefold that of healthy controls (Russell, 1998; Russell & Bieber, 2006). Substance P, along with excitatory amino acids, such as glutamate and aspartate, enhance the transmission of pain through the primary afferent neurons (Larson, Giovengo, Russell, & Michalek, 2000). Increased levels of substance P can induce hyperalgesia and allodynia by lowering the firing threshold of spinal cord neurons and extend long distances from the pain locus resulting in sensitization at sites distant from the pain locus (Bennett, 1999). The proposed neuroplastic changes that result from central sensitization have been visualized in FM patients with functional magnetic resonance imaging (fMRI). Gracely and colleagues (Gracely, Petzke, Wolf, & Clauw, 2002) investigated fMRI changes in FM patients and healthy controls while applying slow, controlled pressure to the thumb nail. When applying 2kg of pressure, FM patients rated the experience as significantly more painful and demonstrated activation of significantly more pain related brain areas as compared to the controls. Research of this kind provides persuasive visual evidence for brain neuroplastic changes in FM patients. Furthermore , a PET study performed without noxious stimuli found a significant hyperperfusion in regions of the brain involved in the

sensory dimension of pain processing, while hypoperfusion was noted in areas associated with the affective-attentional dimension (Guedj, et al., 2007).

A growing body of evidence also indicates that FM is characterized by a dysfunction in descending pain inhibition (Vierck, 2006). Studies report low levels of the serotonin metabolite 5 hydroxy-indoleacetic acid (5HIAA) in the cerobrospinal fluid of FM patients (Russell, Vaeroy, Javors, & Nyberg, 1992) and an overall dysfunction in serotonergic neurotransmission (Coaccioli, et al., 2008). Serotonin plays an important role in modulating the descending inhibitory system. A deficit in the DNIC system, in part modulated by serotonin, of patients with FM adds evidenced to impaired central inhibition in this disorder. Research on DNIC in healthy populations demonstrates that pressure pain thresholds in the leg decrease when inducing ischemic pain in the arm in healthy controls, indicating that pain in the arm activates descending inhibition which inhibits pain in the leg (Kosek & Hansson, 1997). When applying this same procedure to patients with FM, pressure pain thresholds remained the same, indicating a deficit in descending inhibition. These results have been confirmed using a spatial summation procedure in which cold pressor pain to a large area activated descending inhibition in healthy controls but not patients with FM (Julien, Goffaux, Arsenault, & Marchand, 2005). These findings demonstrate that pain inhibitory systems are not effectively activated during spatial summation in patients with FM as compared to healthy controls. Research of this nature provides evidence for abnormalities in both the ascending and descending pathways in patients with FM.

While the presence of central sensitization in FM has been well established, the mechanism by which this sensitization occurs is less clear. As noted, central sensitization occurs due to ongoing C-fiber stimulation, or painful input, resulting in sustained increases in the excitability and responsiveness of neurons in the spinal cord (Zusman, 2002). While pain processing abnormalities such as deficient endogenous pain inhibition (Julien, et al., 2005) have been proposed to enhance the intensity of nociception in patients with FM, research is less clear on the mechanism generating the ongoing nociceptive input needed to initiate central sensitization (Vierck, 2006). Several researchers propose that regional or focal chronic pain might produce the sustained noxious input that results in hypersensitivity of the central nervous system (Bennett, 2005; Lidbeck, 2002; Staud, 2007). This hypothesis proposes that longstanding bombardment of spinal cord neurons by A-beta and C-fibers as a result ongoing focal pain conditions gives rise to the neuroplastic changes characteristic of central sensitization (Meeus & Nijs, 2007; Nielsen & Henriksson, 2007), making regional pain conditions a possible instigator for the altered pain processing of FM. In fact, it has been proposed that regional pain syndromes precede the development of widespread pain in most patients with FM (Nielsen & Henriksson, 2007). This proposal is supported by the fact that FM is frequently associated with several focal pain conditions that also have evidence of being characterized by altered pain processing including TMD, IBS, IC, headaches, back pain, and neck pain (Staud, 2007). These peripheral pain generators could provide the necessary tonic nociceptive input that leads to abnormal pain processing within the central nervous system. Indeed generalized hyperalgesia has been confirmed in several of these disorders. Peripheral sensitization manifests only at the pain locus whereas central sensitization is detected in healthy tissue distant from the pain locus. Hypersensitivity not localized to the area of “injury” indicates underlying changes in the central nervous system that might be explained by central sensitization. Several research studies have reported evidence of centrally mediated pain processing abnormalities in these FM comorbidities.

Tempromandibular joint disorder

A growing body of literature on TMD demonstrates that some individuals with this condition display alterations in central nervous system pain-regulatory systems (Sarlani &

Greenspan, 2005). Individuals with this disorder show enhanced sensitivity to a wide range of experimental pain modalities both at the tempromandibular region and at sites distant from the head and neck region, demonstrating a generalized alteration in nociceptive processing (Maixner, Fillingim, Booker, & Sigurdsson, 1995; Sarlani & Greenspan, 2003). Subjects with TMD display decreased pressure pain thresholds both contralaterally and ipsilaterally to the site of orofacial pain, suggesting the presence of centrally mediated pain (Reid, Gracely, & Dubner, 1994). Subjects with TMD also exhibit enhanced temporal summation to noxious stimuli and impaired central inhibitory mechanisms (Maixner, Fillingim, Sigurdsson, Kincaid, & Silva, 1998) perhaps suggesting an imbalance between descending inhibitory and facilatory pathways in individuals with TMD (Sarlani & Greenspan, 2003). Supporting this notion are separate studies finding that ischemic pain and cold pressor tasks engaged pain inhibitory systems in healthy controls but not subjects with TMD, suggesting dysfunction in the DNIC system (King, et al., 2009; Sigurdsson & Maixner, 1994). Taken together, these findings provide evidence of altered nociceptive processing related to peripheral and central sensitization and impaired descending modulation of pain, similar to mechanisms found in patients with FM. Recent evidence shows that enhanced pain sensitivity may precede and even act as a genetic risk factor for the development of TMD. In a recent prospective cohort study (Diatchenko, et al., 2005), healthy females underwent experimental pain testing and genetic analysis. Analyses demonstrated that single nucleotide polymorphisms (SNPs) of the gene that codes for catecholamine-O-methyltransferase (COMT), an enzyme whose functions include the regulation of levels of catecholamines and enkephalins, was associated with experimental pain sensitivity. Three genetic variants of the COMT gene corresponded with individuals presenting with high pain sensitivity, average pain sensitivity, and low pain sensitivity. The presence of a COMT genetic variant associated with low pain sensitivity decreased an individual's risk of developing TMD by 2.3 times. This study demonstrates that enhanced pain sensitivity in healthy adults predicts the development of TMD and that genetic variations accounting for different levels of catecholamines and enkephalins affects both pain sensitivity and risk of TMD. Future research of this kind is needed to elucidate this relationship in other disorders of pain processing.

Irritable bowel syndrome

Patients with IBS demonstrate similar findings of localized and widespread hypersensitivity. Studies using stimulation of local nociceptors by rectal distention have found reduced local pain thresholds, enlarged referral patterns, and enhanced spinal transmission of nociceptive signals (Coffin, Bouhassira, Sabate, Barbe, & Jian, 2004). Further research illustrates that IBS patients experience cutaneous hypersensitivity extending to cervical and lumbosacral spinal levels (Verne, Robinson, & Price, 2001). These researchers found the most pronounced hyperalgesia at the lumbosacral levels (rectal and foot nociceptive afferents), suggesting that although sensitization occurs throughout the entirety of the nervous system, the hypersensitivity is most profound in the dermatomes closest to the pain locus. As demonstrated in FM and TMD, studies have found dysfunction of DNIC in subjects with IBS. Using a counter-irritation procedure, researchers found that cold pressor pain predicted decreased experimental rectal pain in healthy controls but had no effect in subjects with IBS (Wilder-Smith, Schindler, Lovblad, Redmond, & Nirkko, 2004). Functional MRI scans revealed differences in brain activation between patients and healthy controls, perhaps indicating differences in activation of inhibitory controls.

Interstitial cystitis

Although there have been relatively few psychophysical studies investigating widespread hypersensitivity in IC (Ness, et al., 2005), available evidence supports the hypothesis that

central pain amplification plays a predominant role in maintaining the symptoms of this disorder (Twiss, et al., 2009). As compared to healthy controls, studies show that subjects with IC have significantly lower pressure pain thresholds at the masseter, trapezius, and ulnar muscles and significantly decreased tolerance of ischemic arm pain; demonstrating generalized hypersensitivity to various noxious stimuli (Ness, et al., 2005; van de Merwe, et al., 2008). A recent review (Klumpp & Rudick, 2008) investigating the pathophysiology underlying the pain of IC proposes that peripheral sensitization of bladder C fibers first occurs due to ongoing exposure to sensitizing factors such as histamine, bradykinin, nerve growth factor, and tumor necrosis alpha. Hyperexcitability of peripheral pain fibers leads to persistent activation of spinal cord neurons causing a temporal summation of nocicieptive input that is centrally maintained and no longer needs peripheral input from the bladder. This potential progression leading to the development of generalized hyperalgesia in IC could occur in other regional disorders of pain processing.

Headache

Several psychophysical studies report that sensitization of the central nervous system represents one underlying mechanism in the pathophysiology of headaches (Buchgreitz, Lyngberg, Bendtsen, & Jensen, 2006). This research demonstrates enhanced sensitivity to various modes of painful and non-painful stimuli in individuals with migraines and tension type headaches. For instance, one study found that a portion of migraine headache patients had periorbital cutaneous allodynia in response to non-noxious stimuli (Burstein, Yarnitsky, Goor-Aryeh, Ransil, & Bajwa, 2000). These authors also report findings of allodynia beyond the referred pain area into the ipsilateral head and forearm in a subset of subjects; suggesting hyperexcitability of spinal and supraspinal pain pathways that is characteristic of central sensitization. Findings of widespread hypersensitivity during and outside of migraine attacks adds evidence to the proposition that migrainous central sensitization results as a consequence of increased excitability of medullary dorsal horn neurons which can be sustained despite cessation of peripheral input (de Tommaso, et al., 2002). A recent population study found that a subject's degree of tenderness positively associated with headache frequency (Buchgreitz, et al., 2006). The authors propose that this relation between enhanced pain perception and headache chronicity is due to the development of central sensitization from prolonged nociceptive input, a hypothesis supported by work done in the chronic low back pain (Flor, 2003; Natvig, Bruusgaard, & Eriksen, 2001) and FM (Forseth, Husby, Gran, & Forre, 1999) populations. Fibromyalgia is a common concomitant diagnosis in patients with chronic headache (de Tommaso, et al., 2009).

Chronic low back pain

A substantial amount of work has been done investigating the development of central sensitization in spinal pain disorders such as low back and cervical pain. One group of researchers reported the presence of generalized hyperalgesia in these axial pain disorders by using pressure algometry to assess pressure pain thresholds in patients with chronic low back pain, chronic whiplash pain and healthy controls (Laursen, Bajaj, Olesen, Delmar, & Arendt-Nielsen, 2005). Pressure was systematically applied to seven body locations including sites in the arm, back, finger, and lower leg. They found that patients with spinal pain exhibited significantly lower pressure pain thresholds in all locations as compared to healthy controls. Specific to low back pain a wide body of literature has documented widespread changes in pain processing through experimental pain procedures applied to the back and a peripheral site such as an extremity. These studies have used electrical stimulation (Flor, Diers, & Birbaumer, 2004; Wilder-Smith, Tassonyi, & Arendt-Nielsen, 2002), heat stimuli (Kleinbohl, et al., 1999), and pressure (Clauw, et al., 1999) to demonstrate decreased pain thresholds and tolerance in subjects with low back pain. Patients

with chronic low back pain also display generalized deep tissue hyperalgesia through the use of hypertonic saline induced muscle pain followed by pressure algometry (O'Neill, Manniche, Graven-Nielsen, & Arendt-Nielsen, 2007). This study found that, as compared to controls, individuals with low back pain experienced decreased pressure pain thresholds, higher pain responses, longer duration of pain, and more widespread pain in response to the experimental pain procedure. The authors proposed that the continuous nociceptive input provided by the chronic low back pain might have initiated central sensitization.

Recent imaging studies of chronic low back pain have documented neuroplastic changes in the brain, providing further evidence of altered physiologic processing at the supraspinal level. Functional MRI (fMRI) testing on subjects with idiopathic low back pain and healthy controls demonstrated that 2 kilograms (kg) of pressure at the thumbnail in the healthy control group caused only mild pain and resulted in an increase in fMRI signaling at only one pain-related cortical region (Giesecke, et al., 2004). This same amount of pressure applied to subjects with low back pain resulted in moderate pain and produced increased fMRI signaling at five pain related brain regions. Another group has used magnetic source imaging to document enhanced cortical reactivity and an expansion of cortical representation in response to nociceptive input in patients with chronic back pain (Flor, 2003; Flor, Braun, Elbert, & Birbaumer, 1997). This research showed increased cortical reactivity which correlated with increased duration of pain; furthermore the cortical representation of the back was enlarged in patients with chronic back, such that representation of the back extended into neighboring cortical areas such as the leg and foot.

Chronic neck pain

Similar to studies documenting widespread hyperalgesia and central sensitization in chronic low back pain, several reports document altered pain processing in individuals with chronic neck pain. Psychophysical testing has demonstrated enhanced sensitivity to stimuli within the cervical region and periphery when applying pressure pain (Banic, et al., 2004; Herren-Gerber, et al., 2004; Koelbaek Johansen, Graven-Nielsen, Schou Olesen, & Arendt-Nielsen, 1999), electrical stimulation (Curatolo, et al., 2001; Sheather-Reid & Cohen, 1998), and thermal stimulation (Johnston, Jimmieson, Jull, & Souvlis, 2008). Taken together these studies demonstrate that tonic pain from a peripheral source may result in abnormal central pain processing, such that hypersensitivity is no longer dependent on peripheral input or confined to a particular region of the body (Staud, 2007; Vierck, 2006). The demonstration of decreased pain tolerance and thresholds, hyperalgesia, and allodynia at both focal pain and healthy tissue sites suggest maintenance of sensitization through central rather than peripheral mechanisms.

The demonstration of central sensitization in some individuals with regional pain disorders provides a putative unifying factor between some focal pain syndromes and the widespread pain of FM. It is likely that in some individuals, changes in central pain processing in regional pain states summate to become widespread. Thus contemporary notions of chronic pain states, posits a continuum of pain ranging from focal to widespread. On one end of the continuum is pain that is well localized, perhaps of shorter duration and on the opposite end of the spectrum lies pain that has become chronic and widespread (Macfarlane, 1999). Indeed, several studies have reported the emergence of CWP and FM from chronic low back or neck pain. The frequency with which post whiplash injury patients develop CWP has been reported from between eight percent (Wynne-Jones, Jones, Wiles, Silman, & MacFarlane, 2006) to 21% (Holm, et al., 2007) while another study reported that 22% (Buskila, 1997) developed FM post-injury. One study investigating the development of FM from chronic low back pain reported that 24.5% of subjects transitioned to FM (Lapossy, et al., 1995). Similarly, research has shown that 15% (Macfarlane, et al., 1999) to 32% (Mayer,

Towns, Neblett, Theodore, & Gatchel, 2008) of patients presenting with chronic low back pain met American College of Rheumatology (ACR) diagnostic criteria for FM. Evidence of the development of CWP or FM from a regional pain disorder taken together with research documenting the presence of central sensitization within several focal pain conditions provides support for a continuum of pain ranging from local to widespread.

A unifying hypothesis

A persuasive body of evidence now demonstrates that sensitization represents a unifying pathophysiological mechanism among these painful disorders. It has been proposed that these syndromes have more in common than previously thought, specifically that they are characterized by a dysregulation of peripheral afferents and central nervous system pathways. Given the shared pathopyhsiological mechanisms, these disorders have been coined “central sensitivity syndromes” (CSS) (Yunus, 2008). This underlying connection may not only explain why individuals with these peripheral disorders sometimes develop widespread hyperalgesia, but could also provide the rationale for why CSS often overlap with one another (Vierck, 2006). Epidemiological studies have demonstrated that 75% of patients with FM met TMD criteria and 18% of TMD patients met FM criteria (Plesh, Wolfe, & Lane, 1996) while 32% of FM patients presented with IBS and 32% of patients with IBS met criteria for FM (Sperber, et al., 1999). Similarly 55% of FM patients in one study presented with tension headaches (Campbell, Clark, Tindall, Forehand, & Bennett, 1983). While further research is needed to conclusively establish the precise mechanisms of altered pain processing in these syndromes and explore the presence of central sensitization in other pain disorders (Yunus, 2007), increased research is needed to understand who is at risk for the development of centrally mediated pain disorders. The contemporary hypothesis posits that these disorders emerge in an individual patient when a complex interaction of genetic predisposition, enhanced pain perception, and heightened psychological distress combine with certain environmental factors (Diatchenko, et al., 2006). Some caution as regards to the generalizabilty of the “central sensitization syndrome” tag is warranted, as these individual syndromes present as focal pain complaints. For instance, interstitial cystitis has characteristic diagnostic features at cystoscopy in terms of punctuate vascular glomerulations, pain on hydrodistention and morphologic findings in bladder biopsies (van de Merwe, et al., 2008). This may well imply that each individual CSS is driven by a specific peripheral pain generator. Further research recognizing the complex interplay between genetics, peripheral pain generators, dysfunctional pain processing, psychological factors and environment triggers will be integral to understanding why a subset of individuals develop chronic pain syndromes characterized by abnormal pain processing and why a portion of those patients with localized pain disorders go onto develop WSP or FM.

In summary, a wide body of research evidence has persuasively demonstrated a connection between FM and some regional pain disorders; namely the development of altered pain processing. An increased understanding of the basic pathophsyiological mechanisms shared by these pain disorders now permits a paradigm shift where research and treatment findings in one central sensitivity syndrome might be applied to other syndromes. Collaboration among researchers and clinicians interested in these disorders will not only accelerate progress in developing mechanistic models but also assist in recognizing common risk factors for regional central sensitivity syndromes and widespread pain disorders such as FM. Since CSS are the most common conditions a future physician will treat (Yunus, 2008), expanding insights into these perplexing disorders will positively affect the healthcare community in general.

Acknowledgments

L.L. Kindler was supported by NINR 1 F31 NR010301-01 and NINDS training grant NS045551 to the Comprehensive Center for Pain Research at the University of Florida.

References

Aggarwal VR, McBeth J, Zakrzewska JM, Lunt M, Macfarlane GJ. The epidemiology of chronic syndromes that are frequently unexplained: Do they have common associated factors? International Journal of Epidemiology 2006;35(2):468–476. [PubMed: 16303810]

Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, et al. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. Pain 2004;107(1–2):7–15. [PubMed: 14715383]

Benedetti F. Placebo analgesia. Neurological Sciences 2006;27(Suppl 2):S100–102. [PubMed: 16688609]

Bennett R. Fibromyalgia: From present to future. Current Rheumatology Reports 2005;7(5):371–376. [PubMed: 16174485]

Bennett RM. Emerging concepts in the neurobiology of chronic pain: Evidence of abnormal sensory processing in fibromyalgia. Mayo Clin Proc 1999;74(4):385–398. [PubMed: 10221469]

Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Frequency of headache is related to sensitization: A population study. Pain 2006;123(1–2):19–27. [PubMed: 16630694]

Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. Annals of Neurology 2000;47(5):614–624. [PubMed: 10805332]

Buskila D, Neumann L, Vaisberg G, Alkalay D, Wolfe F. Increased rates of fibromyalgia following cervical spine injury: A controlled study of 161 cases of traumatic injury. Arthritis and Rheumatism 1997;40(3):446–452. [PubMed: 9082932]

Campbell CM, France CR, Robinson ME, Logan HL, Geffken GR, Fillingim RB. Ethnic differences in diffuse noxious inhibitory controls. Journal of Pain 2008;9(8):759–766. [PubMed: 18482870]

Campbell SM, Clark S, Tindall EA, Forehand ME, Bennett RM. Clinical characteristics of fibrositis: A blinded, controlled study of symptoms and tender points. Arthritis and Rheumatism 1983;26(7): 817–824. [PubMed: 6347207]

Clauw DJ, Williams D, Lauerman W, Dahlman M, Aslami A, Nachemson AL, et al. Pain sensitivity as a correlate of clinical status in individuals with chronic low back pain. Spine 1999;24(19):2035–2041. [PubMed: 10528381]

Coaccioli S, Varrassi G, Sabatini C, Marinangeli F, Giuliani M, Puxeddu A. Fibromyalgia: Nosography and therapeutic perspectives. Pain Practice 2008;8(3):190–201. [PubMed: 18373513]

Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: Review of clinical and experimental evidence. Pain 1993;52:259–285. [PubMed: 7681556]

Coffin B, Bouhassira D, Sabate JM, Barbe L, Jian R. Alteration of the spinal modulation of nociceptive processing in patients with irritable bowel syndrome. Gut 2004;53(10):1465–1470. [PubMed: 15361496]

Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Giani C, Zbinden AM, Radanov BP. Central hypersensitivity in chronic pain after whiplash injury. Clinical Journal of Pain 2001;17(4):306–315. [PubMed: 11783810]

Dadabhoy D, Crofford LJ, Spaeth M, Russell IJ, Clauw DJ. Biology and therapy of fibromyalgia. Evidence-based biomarkers for fibromyalgia syndrome. Arthritis Research & Therapy 2008;10(4): 211. [PubMed: 18768089]

de Tommaso M, Guido M, Libro G, Losito L, Sciruicchio V, Monetti C, et al. Abnormal brain processing of cutaneous pain in migraine patients during the attack. Neuroscience Letters 2002;333(1):29–32. [PubMed: 12401553]

de Tommaso M, Sardaro M, Serpino C, Costantini F, Vecchio E, Pia Prudenzano M, et al. Fibromyalgia comorbidity in primary headaches. Cephalalgia 2009;29(4):453–464. [PubMed: 19170692]

Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders: Pathways of vulnerability. Pain 2006;123(3):226–230. [PubMed: 16777329]

Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Human Molecular Genetics 2005;14(1):135–143. [PubMed: 15537663]

Eide PK. Wind-up and the NMDA receptor complex from a clinical perspective. European Journal Of Pain 2000;4:5–17. [PubMed: 10833550]

Flor H. Cortical reorganisation and chronic pain: Implications for rehabilitation. Journal of Rehabilitation Medicine 2003;(41 Suppl):66–72. [PubMed: 12817660]

Flor H, Braun C, Elbert T, Birbaumer N. Extensive reorganization of primary somatosensory cortex in chronic back pain patients. Neuroscience Letters 1997;224(1):5–8. [PubMed: 9132689]

Flor H, Diers M, Birbaumer N. Peripheral and electrocortical responses to painful and non-painful stimulation in chronic pain patients, tension headache patients and healthy controls. Neuroscience Letters 2004;361(1–3):147–150. [PubMed: 15135915]

Forseth KO, Husby G, Gran JT, Forre O. Prognostic factors for the development of fibromyalgia in women with self-reported musculoskeletal pain. A prospective study. Journal Of Rheumatology 1999;26(11):2458–2467. [PubMed: 10555910]

Gebhart GF. Descending modulation of pain. Neuroscience & Biobehavioral Reviews 2004;27(8): 729–737. [PubMed: 15019423]

Giesecke T, Gracely RH, Grant MA, Nachemson A, Petzke F, Williams DA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis & Rheumatism 2004;50(2):613–623. [PubMed: 14872506]

Giovengo SL, Russell IJ, Larson AA. Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia. Journal of Rheumatology 1999;26(7):1564–1569. [PubMed: 10405946]

Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis & Rheumatism 2002;46(5):1333–1343. [PubMed: 12115241]

Guedj E, Taieb D, Cammilleri S, Lussato D, de Laforte C, Niboyet J, et al. Tc-99m-ECD brain perfusion SPECT in hyperalgesic fibromyalgia. European Journal of Nuclear Medicine and Molecular Imaging 2007;34(1):130–134. [PubMed: 16933135]

Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: Specificity, recruitment and plasticity. Brain Research Reviews 2009;60(1):214–225. [PubMed: 19146877]

Herren-Gerber R, Weiss S, Arendt-Nielsen L, Petersen-Felix S, Di Stefano G, Radanov BP, et al. Modulation of central hypersensitivity by nociceptive input in chronic pain after whiplash injury. Pain Medicine 2004;5(4):366–376. [PubMed: 15563322]

Holm LW, Carroll LJ, Cassidy JD, Skillgate E, Ahlbom A. Widespread pain following whiplash-associated disorders: Incidence, course, and risk factors. Journal of Rheumatology 2007;34(1): 193–200. [PubMed: 17143964]

Johnston V, Jimmieson NL, Jull G, Souvlis T. Quantitative sensory measures distinguish office workers with varying levels of neck pain and disability. Pain 2008;137(2):257–265. [PubMed: 17964075]

Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 2005;114:295–302. [PubMed: 15733656]

King CD, Wong F, Currie T, Mauderli AP, Fillingim RB, Riley JL. Deficiency in endogenous modulation of prolonged heat pain in patients with Irritable Bowel Syndrome and Temporomandibular Disorder. Pain 2009;143(3):172–178. [PubMed: 19278784]

Kleinbohl D, Holzl R, Moltner A, Rommel C, Weber C, Osswald PM. Psychophysical measures of sensitization to tonic heat discriminate chronic pain patients. Pain 1999;81(1–2):35–43. [PubMed: 10353491]

Klumpp DJ, Rudick CN. Summation model of pelvic pain in interstitial cystitis. Nature Clinical Practice Urology 2008;5(9):494–500.

Koelbaek Johansen M, Graven-Nielsen T, Schou Olesen A, Arendt-Nielsen L. Generalised muscular hyperalgesia in chronic whiplash syndrome. Pain 1999;83(2):229–234. [PubMed: 10534594]

Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. Pain 1997;70(1):41–51. [PubMed: 9106808]

Lapossy E, Maleitzke R, Hrycaj P, Mennet W, Muller W. The frequency of transition of chronic low back pain to fibromyalgia. Scandinavian Journal of Rheumatology 1995;24(1):29–33. [PubMed: 7863275]

Larson AA, Giovengo SL, Russell IJ, Michalek JE. Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: Implications for nitric oxide pathways. Pain 2000;87(2):201–211. [PubMed: 10924813]

Latremoliere A, Woolf CJ. Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. The Journal of Pain 2009;10(9):895–926. [PubMed: 19712899]

Laursen BS, Bajaj P, Olesen AS, Delmar C, Arendt-Nielsen L. Health related quality of life and quantitative pain measurement in females with chronic non-malignant pain. European Journal of Pain 2005;9(3):267–275. [PubMed: 15862476]

Lidbeck J. Central hyperexcitability in chronic musculoskeletal pain: A conceptual breakthrough with multiple clinical implications. Pain Research & Management 2002;7(2):81–92. [PubMed: 12185372]

Macfarlane GJ. Generalized pain, fibromyalgia and regional pain: An epidemiological view. Best Practice & Research in Clinical Rheumatology 1999;13(3):403–414.

Macfarlane GJ, Thomas E, Croft PR, Papageorgiou AC, Jayson MIV, Silman AJ. Predictors of early improvement in low back pain amongst consulters to general practice: The influence of pre-morbid and episode-related factors. Pain 1999;80(1–2):113–119. [PubMed: 10204723]

Maixner W, Fillingim R, Booker D, Sigurdsson A. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain. Pain 1995;63(3):341–351. [PubMed: 8719535]

Maixner W, Fillingim R, Sigurdsson A, Kincaid S, Silva S. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: Evidence for altered temporal summation of pain. Pain 1998;76(1–2):71–81. [PubMed: 9696460]

Marchand S. The physiology of pain mechanisms: From the periphery to the brain. Rheumatic Diseases Clinics of North America 2008;34(2):285–309. [PubMed: 18638678]

Mayer DJ, Wolfle TL, Akil H, Carder B, Liebeskind JC. Analgesia from electrical stimulation in the brainstem of the rat. Science 1971;174(16):1351–1354. [PubMed: 5167502]

Mayer TG, Towns BL, Neblett R, Theodore BR, Gatchel RJ. Chronic widespread pain in patients with occupational spinal disorders: Prevalence, psychiatric comorbidity, and association with outcomes. Spine 2008;33(17):1889–1897. [PubMed: 18670343]

Meeus M, Nijs J. Central sensitization: A biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. Clinical Rheumatology 2007;26(4):465–473. [PubMed: 17115100]

Mendell LM. Physiological properties of unmyelinated fiber projection to the spinal cord. Experimental Neurology 1966;16:316–332. [PubMed: 5928985]

Natvig B, Bruusgaard D, Eriksen W. Localized low back pain and low back pain as part of widespread musculoskeletal pain: Two different disorders? A cross-sectional population study. Journal Of Rehabilitation Medicine 2001;33(1):21–25. [PubMed: 11480465]

Ness TJ, Powell-Boone T, Cannon R, Lloyd LK, Fillingim RB. Psychophysical evidence of hypersensitivity in subjects with interstitial cystitis. Journal of Urology 2005;173(6):1983–1987. [PubMed: 15879797]

Nielsen LA, Henriksson KG. Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): The role of central and peripheral sensitization and pain disinhibition. Best Practice & Research in Clinical Rheumatology 2007;21(3):465–480.

O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L. Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. European Journal of Pain 2007;11(4):415–420. [PubMed: 16815054]

Perrot S, Dickenson AH, Bennett RM. Fibromyalgia: Harmonizing science with clinical practice considerations. Pain Practice 2008;8(3):177–189. [PubMed: 18363616]

Plesh O, Wolfe F, Lane N. The relationship between fibromyalgia and temporomandibular disorders: Prevalence and symptom severity. Journal of Rheumatology 1996;23(11):1948–1952. [PubMed: 8923373]

Porreca F, Ossipov MH, Gebhart GF. Chronic pain and medullary descending facilitation. Trends in Neurosciences 2002;25(6):319–325. [PubMed: 12086751]

Reid KI, Gracely RH, Dubner RA. The influence of time, facial side, and location on pain-pressure thresholds in chronic myogenous temporomandibular disorder. Journal of Orofacial Pain 1994;8(3):258–265. [PubMed: 7812223]

Russell IJ. Advances in fibromyalgia: Possible role for central neurochemicals. American Journal of the Medical Sciences 1998;315(6):377–384. [PubMed: 9638894]

Russell, IJ.; Bieber, CS. Myofascial pain and fibromyalgia syndrome. In: McMahon, SB.; Koltzenburg, M., editors. Wall and Melzack's Textbook of Pain. 5th ed.. Elsevier Churchill Livingstone; Philadelphia: 2006. p. 669-681.

Russell IJ, Vaeroy H, Javors M, Nyberg F. Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. Arthritis & Rheumatism 1992;35:550–556. [PubMed: 1374252]

Sarlani E, Greenspan JD. Evidence for generalized hyperalgesia in temporomandibular disorders patients. Pain 2003;102(3):221–226. [PubMed: 12670662]

Sarlani E, Greenspan JD. Why look in the brain for answers to temporomandibular disorder pain? Cells Tissues Organs 2005;180(1):69–75. [PubMed: 16088135]

Sheather-Reid RB, Cohen ML. Psychophysical evidence for a neuropathic component of chronic neck pain. Pain 1998;75(2–3):341–347. [PubMed: 9583770]

Sigurdsson A, Maixner W. Effects of experimental and clinical noxious counterirritants on pain perception. Pain 1994;57(3):265–275. [PubMed: 7936706]

Sperber AD, Atzmon Y, Neumann L, Weisberg I, Shalit Y, Abu-Shakra M, et al. Fibromyalgia in the irritable bowel syndrome: Studies of prevalence and clinical implications. AMerican Journal of Gastroenterology 1999;94:3541–3546. [PubMed: 10606316]

Staud R. Future perspectives: Pathogenesis of chronic muscle pain. Best Practice & Research in Clinical Rheumatology 2007;21(3):581–596.

Staud R, Domingo M. Evidence for abnormal pain processing in fibromyalgia syndrome. Pain Medicine 2001;2(3):208–215. [PubMed: 15102253]

Staud R, Price DD, Robinson ME, Mauderli AP, Vierck CJ. Maintenance of windup of second pain requires less frequent stimulation in fibromyalgia patients compared to normal controls. Pain 2004;110(3):689–696. [PubMed: 15288410]

Staud R, Rodriguez ME. Mechanisms of disease: Pain in fibromyalgia syndrome. Nature Clinical Practice Rheumatology 2006;2(2):90–98.

Suzuki R, Rygh LJ, Dickenson AH. Bad news from the brain: Descending 5-HT pathways that control spinal pain processing. Trends in Pharmacological Sciences 2004;25(12):613–617. [PubMed: 15530638]

Tracey I, Dunckley P. Importance of anti- and pro-nociceptive mechanisms in human disease. Gut 2004;53(11):1553–1555. [PubMed: 15479668]

Twiss C, Kilpatrick L, Craske M, Buffington CA, Ornitz E, Rodriguez LV, et al. Increased startle responses in interstitial cystitis: Evidence for central hyperresponsiveness to visceral related threat. Journal of Urology 2009;181(5):2127–2133. [PubMed: 19286199]

Urban MO, Gebhart GF. Central mechanisms in pain. Medical Clinics of North America 1999;83(3):585–596. [PubMed: 10386116]

van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: An ESSIC proposal. European Urology 2008;53(1):60–67. [PubMed: 17900797]

Verne GN, Robinson ME, Price DD. Hypersensitivity to visceral and cutaneous pain in the irritable bowel syndrome. Pain 2001;93(1):7–14. [PubMed: 11406333]

Vierck JCJ. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). Pain 2006;124(3):242–263. [PubMed: 16842915]

Wilder-Smith CH, Schindler D, Lovblad K, Redmond SM, Nirkko A. Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. Gut 2004;53(11):1595–1601. [PubMed: 15479679]

Wilder-Smith OH, Tassonyi E, Arendt-Nielsen L. Preoperative back pain is associated with diverse manifestations of central neuroplasticity. Pain 2002;97(3):189–194. [PubMed: 12044615]

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis & Rheumatism 1990;33(2):160–172. [PubMed: 2306288]

Wynne-Jones G, Jones GT, Wiles NJ, Silman AJ, MacFarlane GJ. Predicting new onset of widespread pain following a motor vehicle collision. Journal Of Rheumatology 2006;33(5):968–974. [PubMed: 16541476]

Yunus MB. Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. Best Practice & Research in Clinical Rheumatology 2007;21(3): 481–497.

Yunus MB. Central sensitivity syndromes: A new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Seminars in Arthritis & Rheumatism 2008;37(6):339–352. [PubMed: 18191990]

Zusman M. Forebrain-mediated sensitization of central pain pathways: ‘Non-specific’ pain and a new image for MT. Manual Therapy 2002;7(2):80–88. [PubMed: 12151244]