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Editorial Review: An Update on Central Sensitivity Syndromes and the Issues of Nosology and Psychobiology

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Abstract: Central sensitization (CS), simply defined as an amplified response of the central nervous system to peripheral input, is a concept of great importance in clinical medicine. It has helped to explain aspects of the pathophysiology of common diseases, e.g. fibromyalgia syndrome (FMS), irritable bowel syndrome, vulvodynia, headaches, chronic pelvic pain and other overlapping conditions (collectively called central sensitivity syndromes, or CSS). It also applies to pain of complex regional pain syndrome, osteoarthritis (OA), rheumatoid arthritis (RA) and post-operative pain. The pathology-pain gap in CSS is readily explained by CS. Many FMS and other CSS patients have peripheral pathology, e.g. nociceptive areas in the muscles, arthritis, small fiber neuropathy and inflammation. Pro-inflammatory cytokines are elevated in some patients. Identification of CS in patients with structural pathology, e.g. OA and RA, has helped to explain why not all patients benefit from nonsteroidal anti-inflammatory drugs or joint replacement surgery, and require therapy directed at CS. Glial cells are important in pain processing. Remarkable advances have been achieved in neuroimaging, including visualization of grey matter and white matter, not only during provoked pain but also pain at rest. Based on CS mechanisms, targeted individual therapy may now be possible. Appropriate nosology is important particularly for effective patient care. Dichotomy of neurochemical-structural ("functional") and structural ("organic") pathology should be abandoned; many patients have both. Psychobiology is also biology. Patient-blaming terms like somatization, somatizer and catastrophizing should be avoided. For therapy, both pharmacological and non- pharmacological approaches are important, including recognition of subgroups and person/patient-centered care.

Keywords: Central sensitization, central sensitivity syndromes, fibromyalgia, nosology, overlapping syndromes, psychology, somatization, peripheral pathology, small fiber neuropathy, chronic pain, functional syndromes.

INTRODUCTION

In this important thematic issue of Current Rheumatology Reviews (CRR), knowledgeable authors have contributed on different aspects of central sensitivity syndromes (CSS) under "one roof." Given that many physicians are not adequately familiar with the important concept of central sensitization (CS) in general, this is a timely publication where various diseases of the CSS family e.g. fibromyalgia syndrome (FMS), irritable bowel syndrome (IBS), myofascial temporomandibular disorder (TMD), tension-type headache, migraine, chronic pelvic pain (CPP) in male and female, restless legs syndrome (RLS) and chemical intolerance (CI) (multiple chemical sensitivity) have been discussed. As has been described in detail [1], CS is one of the significant pathophysiological mechanisms that bind the CSS diseases.

Taken together, CSS are likely to be the most common reason for patient visits in an outpatient clinic. Precise prevalence of CSS in the USA is not known. Approximately 100 million adults in the USA suffer from chronic pain according to a study by the Institute of Medicine [2]. Based on this figure, and given that many more conditions besides those included in this article may be classified as having a CSS condition in the future, one may estimate that 25-30 million adults in the USA suffer from one or more CSS conditions. Thus a better understanding of the pathophysiological mechanisms of these common conditions leading to better management is a moral imperative.

I proposed this thematic issue because of an absence of satisfactory current information on CSS all in one convenient volume. This special issue is meant to benefit physicians in practice who will have a general interest in pathophysiology and who will frequently encounter CSS patients. I hope it will also be useful for the academicians and researchers. It should also serve the purpose of teaching the young minds.

In this editorial, I shall provide general information about CS and an updated overview of CSS diseases, referring to the articles written by knowledgeable contributors in the two-volume thematic issue of CRR. I shall start with a sketch of the contents of the two separate issues of CRR. The first volume contains several basic subjects related to CSS, e.g. pathophysiology of CS partly covered in this article and partly by Drs. Richard Gracely and Petra Schweinhardt. This volume also contains cytokine and immune system related to CSS, person-centered management of FMS, psychosocial factors and description of several diseases, e.g. FMS, CPP in females and CI. .

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The second volume discusses neuroimaging of CSS, psychosocial vulnerability, myofascial TMD, tension type headaches and migraine, RLS and periodic limb movements, male CPP and general management aspects, e.g., cognitive behavioral therapy (CBT). Pharmacological treatment has been discussed in individual diseases. Despite the fact that chronic fatigue syndrome (CFS) (systemic exertion intolerance disease) clinically overlaps with other members of the CSS family, definitive evidence of CS in this disease (excluding those having pain) is lacking, and was, therefore, not included. Same is true of posttraumatic stress disorder that has limited evidence for CS.

Drs. Gracely and Schweinhardt propose a new conceptual model for CSS in their article "Programmed symptoms: disparate effects united by purpose" that also succinctly incorporates roles of sympathetic nervous system, HPA-axis, immune system along with proinflammatory cytokines, and the roles of stress and behavior response [3]. Cytokines and immune system in CSS are further discussed by Dr. Roland Staud [4]. Dr. Gareth Jones evaluates early life adversity as risk factors for CSS [5].

The paper by Drs Gracely and Schweinhardt focuses our attention to the acute and subacute stages of an event that may lead to CSS. The examples include acute musculoskeletal injury, acute viral or bacterial infection, acute psychological stress and early neuropathic symptoms (e.g. tingling and numbness) resulting from small fiber neuropathy (SFN) that is now well- documented in several CSS diseases. The authors suggest that such an event promotes quiescence for the purpose of healing. Implicit in this suggestion is the need for active intervention, e.g. non-steroidal anti-inflammatory drugs (NSAIDs), physical therapy (heat, stretching), topical analgesics, tender/trigger point injection, antibiotic if indicated and stress reduction—depending on the event or situation. Such an action plan has so far not been emphasized in the literature. Such management may prevent chronification and maladaptive behavior [6].

Dr. Brian Walitt and his colleagues critically and elaborately reviewed various brain imaging techniques and the results of imaging studies in several CSS conditions [7] (second volume). They discuss findings at rest and on evoked pain stimulation. They also review treatment effects and comment on the current technical limitations.

In this editorial, I shall briefly discuss CS in general and CS in diseases with classical structural pathology (e.g. inflammatory, degenerative, infective, neuropathic and neoplastic). Further, I shall update information on aspects of CSS and also comment on the important issues of nosology and psychobiology in these disorders.

CENTRAL SENSITIZATION

The term central sensitization (CS) was coined in 1989 by Clifford Woolf and his colleagues based on their work in the rat model, showing hyperexcitability of the spinal cord neurons evoked by peripheral tissue injury [8]. Whether an individual needs an active peripheral input to maintain CS has been discussed in the literature [3]. According to Woolf, "Sentiment swings from CS absolutely requiring an afferent input to one where it can be completely autonomous—both are likely correct—my sense is low levels of input can sustain or increase CS but they are not necessary" (personal communication). Independently, I agree with this statement. Similar opinion was voiced by Woolf in a review paper in 2011 [9].

The term CS has been used in the clinical context to explain widespread hyperalgesia and allodynia to a host of physical stimuli [1, 9] and also to hypersensitivity to environmental stimuli, e.g. auditory, chemicals and light [1].

Physiologically, CS may be defined as a state of hyperexcitement of the central nervous system (CNS) involving the spinal and supraspinal structures due to an amplification of neural signaling involving various synaptic and neurotransmitter activities (see below) irrespective of a defined peripheral input [1, 9].

Structural, functional and molecular changes are associated with CS. Complex molecular changes have been discussed by Kuner [10]. At a very simplistic level, A-delta and C nociceptive fibers are activated by products of inflammation, e.g. bradykinin, substance P (SP) and prostaglandin at the periphery. These fibers along with non-noxious A-beta fibers converge at wide dynamic range neurons at the dorsal horn of the spinal cord. Following a peripheral stimulus, A-delta and C fibers release SP, calcitonin gene-related peptide (CGRP), glutamate, aspartate, nerve growth factor (NGF) and others at the afferent nerve endings into the synaptic cleft. This is accompanied by a barrage of impulses that activate the post-synaptic receptors, e.g. SP activates neurokinin 1 (NK 1) receptors, glutamate activates several receptors, e.g. N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) and metabotropic glutamate (mGlu), and NGF activates tyrosine kinase B (Trk-B) receptors. Activation of NMDA receptors is followed by various cellular changes, e.g. increased membrane permeability, entry of intracellular calcium, activation of protein kinase and expression of c-fos. These changes cause escalation of the hyperexcitability of the secondary neurons with marked amplification of the peripheral stimulus. These neurons ascend to thalamus, hypothalamus, the limbic system and finally to somatosensory cortex.

CS is the balance between pain transmission and pain inhibition. While the ascending pathway is involved in neurotransmission causing pain, pain inhibition is mediated mostly by serotonin, norepinephrine, enkephalins, gamma-amino-butyric acid and dopamine via descending pathways. CS is further influenced by facilitatory neurons in the descending pathways, local interneurons in the spinal cord and various supraspinal structures described above. Besides the sensory aspect, the affective dimension of pain (unpleasantness, emotional reaction) is determined by the limbic system structures e.g. anterior cingulate cortex (ACC) and central nucleus of amygdala [1, 9, 10].

A phenomenon related to CS is temporal summation (TS) in which repeated identical stimulation produces progressively increased perception of pain on each successive stimulus; this is akin to wind-up phenomenon in animals [9]. TS is mediated by NMDA receptors that can be targeted by drugs in management of pain [9].

In recent years, the important roles of glial cells [11] and brain-derived neurotrophic factor (BDNF) [6, 11] in CS have been underscored. BDNF, purified in 1982, plays an important role in neural growth and cell survival. It also significantly contributes to CS by strengthening excitatory and weakening inhibitory synapses. It acts at all levels of pain pathway—peripheral, spinal and supraspinal [6]. At the brain level, it acts on both descending facilitatory and inhibitory neurons [6]. It also holds promise for a therapeutic target [6].

Glial activation, mostly by nerve injury, neuropathies, inflammation, cancer and chronic opioid therapy, results in release of glial mediators, e.g. cytokines (TNF-alpha, IL-6, IL-1beta,) growth factors (e.g. BDNF) and proteases; these mediators have both excitatory and inhibitory synaptic transmission. Their action is indirect via a synergestic neuro-glial interaction. Secondary amplification takes place through the actions of pro-inflammatory cytokines [11].

Clinically, CS is characterized by excessive sensitivity to a host of peripheral noxious stimuli, e.g. pressure, heat, cold, ischemia, hypertonic saline and electricity as well as non-noxious stimuli, e.g. touch and gentle rubbing. This is accompanied by an unpleasant after-stimulus sensation, e.g. burning, throbbing and paresthesia. The hypersensitivity extends beyond the territory of a nerve stimulated or injured producing expansion of receptive field, including bilateral involvement in case of unilateral nociceptive stimulus or injury [1, 9]. CS patients with chronic pain are also sensitive to sound, chemicals and light [1, 6].

The term CS has been used in recent years to describe secondary hyperalgesia (hypersensitivity of the area surrounding the site of injury) and sites further distant as described in lateral epicondylalgia [12], chronic patellar tendinopathy [13] and carpal tunnel syndrome [14]. CS has also been described in a wide variety of diseases with classical structural pathology, e.g. rheumatoid arthritis (RA), osteoarthritis (OA) and connective tissue diseases [15, 16], diabetes mellitus, juvenile chronic arthritis [15], Parkinson's disease [17], multiple sclerosis [18], peripheral neuropathy [19], cancer [20] and joint replacement surgery [21, 22]. Some of these diseases are associated with FMS [15] having multiple widespread tender points, indicative of CS. Thus, use of the nosology CS is broad in the context of CSS as well as other diseases with structural pathology, e.g. OA.

SHOULD THE TERM CENTRAL SENSITIZATION BE USED IN CLINICAL MEDICINE?

Because evidence for distant spread of hyperexcitability in the CNS beyond the area of secondary hyperalgesia in the presence of sustained afferent input was lacking in the original animal model [8], Hansson [23] raises objection to use of the term central sensitization in the clinical context where hyperalgesia is of widespread distribution and a peripheral nociceptive input is not always obvious. He suggests alternative nomenclatures, e.g. the generic term of "hypersensitivity," and "cognitive-emotional sensitization" that was originally suggested by Brosschot [24]. Gracely and Schweinhardt have similar questions [3]. Brosschot's hypothesis is entirely a psychobiological one, based on the model of anxiety that is present in a minority of CSS condition, e.g. FMS [25]. There is no evidence that depression can alter the nociceptive neuronal threshold towards hyperexcitement [1]. In an accompanying editorial, Woolf defends using the term CS in chronic pain conditions [26], noting a lack of evidence for cognitive-emotional sensitization alone in widespread pain. He further states that the International Association for the Study of Pain (IASP) definition of CS, "increased responsiveness of nociceptive neurons in the CNS to their normal or sub-threshold afferent input," does not include sustained input from the periphery.

Phillips and Clauw [16] suggest use of other terms, e.g. 'central pain,' 'central augmentation' and 'central amplification' instead of CS, giving a similar logic that the term CS was originally used in the context of a sustained peripheral noxious input in an animal model.

So, the question arises, should we continue to use the term CS in the context of human disease? It is clear that this term has been extensively used in clinical conditions for more than two decades. The term CS was probably first used in the clinical setting in 1993 by Woolf and Chong [27]. I had first used the term CSS in the context of FMS and other overlapping syndromes in 2000 [28].

Characteristics of a disease with a given name may change over time. They may be different from the original description. For example, the original term fibrositis was a regional pain condition, e.g. low back pain (LBP). The origin and the evolution of the term fibrositis to mean something very different in the 1970s and 1980s (e.g. widespread pain, poor sleep and fatigue) have been discussed elsewhere [29]. The description of RA by William Osler in 1892 [30] did not include the systemic manifestations. Thus, the current description of CS in clinical conditions need not be the same as originally described in the animal model [8]. As we will see in the next section, CS plays an important role in CSS and other chronic pain conditions. Given its relevance and usefulness in clinical medicine, I agree with Woolf that the term, central sensitization, should continue to be used [26].

RELEVANCE OF CS IN CSS AND CHRONIC PAIN

It is generally accepted that CS causes pain [31] and it most likely plays a causal role in CSS conditions [1]. CS has helped to better explain aspects of pathophysiological mechanisms and symptoms of many diseases with pain as mentioned above. The concept has been useful in patient management [32, 33]. CS is strongly correlated with pain symptoms [34] and it highly predicts clinical pain intensity [35].

With regard to other symptoms of CSS besides pain, the relationship between CS and poor sleep is likely to be bidirectional. It is known that sleep deprivation causes generalized hyperalgesia to heat, blunt pressure, cold and pinprick stimuli among healthy subjects [36]. Many studies have shown correlations between poor sleep and CS in FMS as measured by tender points [1] and by algometry [37]. Poor sleep is correlated with CS as measured by allodynia and pericranial tenderness in primary headache [38]. CS-induced pain may cause poor sleep.

CS may cause dyscognition (e.g. problems of concentration and memory). Brain structures involved in neurocognition include dorsolateral and medial PFC, ACC and the insula [39, 40], the same structures that are activated by peripheral nociceptive stimulus in CSS [7]. Chronic pain is associated with dyscognition [40].

It seems unlikely, however, that fatigue is caused by CS. In a well-designed study, Geisser, *et al.* evaluated pressure pain sensitivity among 38 patients with FMS or CFS by applying hard rubber probe on the thumbnail using the multiple random staircase method [41]. They found that sensory amplification was not correlated with fatigue. Three studies showing CS in CFS [42-44] failed to exclude patients with musculoskeletal pain or adjust the data statistically for pain. Staud, *et al.* found indirect evidence for sensitization of the fatigue pathways in CFS [43]. In the context of depression (that has little evidence of CS by multiple studies), I had previously suggested the term *hypo*senstitization (to nociceptive stimuli) [1] and they probably belong to a separate category of "central hyposensitivity syndromes." For example, numbers of tender points in depression are *fewer* and pain threshold *higher* than normal controls [1]. Same may be true of chronic fatigue (without accompanying pain), since both fatigue and depressive patients with psychomotor retardation are characterized by inertia, whereas CS is associated with arousal and activity (e.g. moving around or active effort to relieve the pain by rubbing).

Spontaneous pain in CSS (e.g. FMS) may result from a highly sensitized CNS because of genetic vulnerability and neurosensory insult from earlier injuries during the neonatal and childhood periods causing pain and CS [45, 46]. In such cases low level physical stress or injury in daily life (e.g. lifting, gardening or poor posture) is sufficient to maintain high level of CS and cause spontaneous pain. Moreover, CS in FMS is maintained by tonic muscle afferent input related to trigger/ tender points [47].

Yarnitsky suggests pronoceptive and antinociceptive pain modulation profile of healthy and chronic pain patients by evaluating two distinct mechanisms of CS, ie, TS and conditioned pain modulation (CPM) [48]. CPM is the clinical representation of diffuse noxious inhibitory controls in animals. TS is one way of measuring pain facilitation in the CNS while CPM measures pain inhibition [48]. NMDA receptors are involved in TS. Ketamine, among others (e.g. memantine) is a NMDA receptor antagonist.

Enhanced TS has been reported in several CSS diseases, e.g. FMS [49] and TMD [50]. CPM is based on the concept of "pain inhibits pain." First, a test stimulus (e.g. cold or hot water immersion) is applied to a limb, followed by the same stimulus during or soon after a second conditioning stimulus (e.g. thermal, mechanical or electrical) on the opposite limb. The conditioning stimulus inhibits the pain of the test stimulus in normal healthy individuals; the CPM effect is the net change in self-reported pain intensity between the two stimuli [48].

Pain inhibition is mediated by the descending pathway that is integrated by periaqueductal gray (PAG) in the midbrain with input from the spinal cord, medulla and PFC [1,48]. CPM is mediated by serotonin, norepinephrine, GABA and enkephalines via descending pathway [1]. CPM is defective (pain inhibition is attenuated) in CSS conditions, e.g. FM [51] and IBS [52]. Patients with both enhanced TS and malfunctioning CPM are at a greater risk for enhanced CS and clinical pain [48]. CPM is normal in depression [31]. This is an important distinction between FMS and depression.

It is becoming increasingly clear that genetics play a vital role in CS and pain [53-56]. Seltzer comments that nothing in pain makes sense except in the light of genetics [54]. There is a great deal of genetic variability in pain, both in humans [55] and animals [56]. Young, *et al.* found as many as five distinct genes associated with pain sensitivity in a mouse peripheral nerve injury model [56].

Environmental effect on heritability of pain through the mechanisms of gene expression and epigenetics is an important new field [57], but is beyond the scope of this paper.

Does CS cause chronic pain (e.g. CSS) or do the chronic diseases causes CS? I think the answer is both in a circular or bidirectional way (CS→ chronic pain→CS). In a large NIH-funded prospective cohort study, Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA), 202 healthy females were followed for three years. It was found that those with genetically determined enhanced CS were more likely to develop TMD than those without [58]. In their 5 year follow-up cohort of 2,737 TMD-free participants, greater pain sensitivity (ie, CS) was significantly associated with development of TMD [59], suggesting a causal effect of CS.

Pre-operative enhanced TS predicted greater acute pain post-operatively in a thoracotomy cohort [60]. TS was reported to predict analgesic efficacy after Caesarian section; those with enhanced TS responded to ketamine (a drug known to attenuate TS) post-operatively, but those with non-enhanced TS did not respond [61], thus determining the appropriate drug.

In a study of diabetic neuropathy, patients with deficient CPM responded better to duloxetine than those with more efficient CPM [62]. Duloxetine an SNRI (that selectively inhibits reuptake of serotonin and norepinephrine), works on the descending pain inhibitory pathway (hence on CPM) [63].

Pregabalin that reduces calcium influx during depolarization and reduces release of substance P and glutamate [63] and decreases central sensitization [64] has been found to help pain in chronic pancreatitis in a double blind placebo controlled study [65].

SIGNIFICANCE OF CS IN CLINICAL MEDICINE: IMPLICATIONS FOR PAIN MANAGEMENT

A huge shift is taking place in the understanding and management of chronic pain and post-surgical pain based on the pathophysiology of CS. Satisfactory management of these conditions has doggedly eluded us for centuries. While a "cure" of these conditions is beyond our reach at this time, understanding CS has provided us a helpful new approach. Such understanding has been possible because of progress in genetics, neurochemistry, neurophysiology, molecular biology, immunology, neuroimaging as well as structural pathology in the peripheral tissues.

It was always a puzzle, for example, why a significant number of patients continue to have joint pain after joint replacement surgery, for which the surgeons were often blamed in a number of litigations. In a large prospective study of 1217 patients, Scott, *et al.* reported that up to 20% of patients were dissatisfied with the outcome of their total knee replacement surgery [66]. Lundblad, *et al.* found that preoperative low threshold to electric stimulation predicted persistent post-operative pain [67].

Since CS contributes to chronic pain [12-22], its treatment should target CS with centrally acting drugs, e.g., pregabalin, SNRIs and NMDA receptor antagonists [63] as well as centrally acting non-pharmacological therapy e.g., cognitive behavioral therapy (CBT), mindfulness meditation and neuroscience education [63, 68]. New drugs are also being developed based on the pathophysiology of CS [69, 70].

He, *et al.* found significant improvement in both pain and generalized hyperalgesia among patients with endometriosis who had surgery for this disease compared to a control group who did not have surgery [71]. Why majority of patients benefit from elimination of the peripheral nociception generators by surgery while pain continues (or gets worse) in others need further studies. Injection of trigger/ tender points [47, 72] including dry needling [72] may attenuate peripheral afferent input.

Based on observations that psychobiological factors, e.g. stress and anxiety, enhance pain perception, the term 'cognitive emotional sensitization' (CES) has been introduced [24] and discussed [73]. The neural correlates of sensory-discriminative and affective-emotional dimensions of pain have been identified by neuroimaging [73] and hold promise for targeted treatment by psychobiological therapy as mentioned above.

CLASSIFICATION OF CS IN CLINICAL MEDICINE

In the broad categories of acute and chronic CS, CSS as a group [1] is only one variety (Table **1**). Considering space limitation, limited references will be provided. Examples of CS in acute conditions are acute musculoskeletal pain due to injury [74], post-surgical pain [75, 76] and acute viral infection [77, 78] where acute peripheral nociceptive input becomes centralized and may become chronic in some patients (Table **1**).

CS is secondary to, or associated with, diseases with structural pathology [13-20], infections [77-85], and drugs (e.g. opioid therapy) [86]. Opioids actually can cause CS [86]. HIV infection may induce CS by causing neuropathy [19]. There is only indirect evidence for CS associated with, or caused by hepatitis C virus [79, 80], human immunodeficiency virus [80, 81], and *Borrelia burgdogferi* [82]. These conditions are associated with FMS that is a prototypical central sensitivity syndrome [87]. A high tender point (TP) count was found in EB virus infection [78]; TPs were associated with higher temperature at baseline, suggesting the role of infection. One can hypothesize that inflammatory cytokines contributed to CS during the acute phase of the EBV infection [88].

Candida infection is likely to cause local sensitization and CS in vulvodynia [84, 85]. The evidence for E. coli causing CS is based on animal model [83] and a history of repeated urinary infection in interstitial cystitis [89], probably causing peripheral sensitization and providing afferent input for CS.

Table 1. Proposed classification for central sensitization (CS) in clinical medicine.

A.	**Acute**
Physical trauma; nerve injury; post-surgical	
B.	**Chronic**
1.	Primary without an underlying disease
a.	Central sensitive syndromes (CSS), e.g. fibromyalgia, irritable bowel syndrome, restless legs syndrome, headaches
b.	Neurovasomotor diseases--Complex regional pain syndrome
2.	Secondary to well- defined pathology/ disease, infection, drugs, childhood stress and physical trauma
a.	Well defined diseases, e.g. OA, RA, systemic lupus erythematosus, chronic pancreatitis, multiple sclerosis, malignancy, etc.
b.	Infection (may be acute, subacute or chronic)*
	Viruses—e.g. herpes zoster; ? other viruses, e.g. hepatitis C human immunodeficiency and Epstein-Barr virus
	Bacteria—e.g. E. coli, *Borrelia Burgdorferi*
	Fungi—e.g. Candida infection in vulvodynia
c.	Drugs—e.g. morphine
d.	Neonatal and childhood stress (e.g. surgery, inflammation and psychological trauma
e.	Trauma--surgical procedures, physical trauma (accident, etc.)
3.	Neuropathies irrespective of primary or secondary cause #
4.	Poor sleep irrespective of primary or secondary cause #

*Association between CS and infection in the case of hepatitis C virus, human immunodeficiency virus, Epstein-Barr virus and *Borrelia Burgdorferi* is indirect (see text). There is an increased prevalence of fibromyalgia among patients with these infections.

Note that neuropathies and poor sleep have been listed as categories separate from secondary, since these conditions may be both primary and secondary.

Stress can cause CS both in humans and animal models [90-92]. Different mechanisms (e.g. neurotransmission, neuromodulation and neuroendocrine) for stress-induced neural plasticity have been reviewed [90-92]. Neuropathies cause CS [19, 93], as does sleep deprivation [36, 94].

Acute CS and its transition to chronic pain are of paramount importance, since this phase gives us a window to modify the outcome and prevent chronic pain. Three important mechanisms involved in this transition are peripheral sensitization, central sensitization and CPM [95].

CENTRAL SENSITIVITY SYNDROMES (CSS): AN UPDATE

CSS as a Group Nosology vs. Central Sensitivity Syndrome as an Individual Condition

CSS as a group nosology. CSS was defined in 2007 as "comprising an overlapping and similar group of syndromes without structural pathology and are bound by the common mechanism of central sensitization that involves hyperexcitement of the central neurons through various synaptic and neurotransmitter/neurochemical activities" [1]. Since it is now clear that structural pathology may be present in CSS (see next section), the phrase "without structural pathology" is now omitted. Instead, these conditions should be viewed as representing primary i.e. not secondary to, or associated with, another condition as discussed above (see Table **1**). The term 'primary' is preferred to 'idiopathic' since CS is regarded an underlying pathophysiologic mechanism that plays a causal role [31]. 'Idiopathic' has a connotation that 'no cause is known,' which is not true of CSS conditions.

Two criteria were suggested for classification of a disease as a member of the CSS family in 2007: (a) mutual associations between the members ("the clinical glue") and (b) the presence of CS ("the pathophysiological glue") [1, 28]. A third criterion may also be added here: these are primary conditions, not having an underlying diseases, e.g. degenerative and inflammatory diseases (Table **1**). Complex regional pain syndrome (CRPS) will be discussed later.

Current proposed members of the CSS family and central sensitivity syndrome as a primary individual condition are shown in Table **2** and the classification criteria for the CSS

Table 2. Members of the central sensitivity syndromes (CSS) family* and an individual central sensitivity syndrome.**

A.	**CSS family**
1.	Fibromyalgia syndrome
2.	Irritable bowel syndrome
3.	Primary (dysfunctional) dyspepsia
4.	Tension-type headache
5.	Migraine
6.	Myofascial pain syndrome
7.	Myofascial temporomandibular disorder
8.	Primary chronic neck pain
9.	Primary low back pain
10.	Restless legs syndrome
11.	Periodic limb movement disorder
12.	Endometriosis
13.	Primary dysmenorrhea
14.	Painful bladder syndrome/ interstitial cystitis
15.	Vulvodynia/vulvar vestibulitis
16.	Chronic prostatitis/chronic male pelvic pain
17.	Posttraumatic stress disorder
18.	Multiple chemical sensitivity (chemical intolerance)
19.	Primary burning mouth syndrome
20.	Primary chronic cough #
21.	Primary chronic tinnitus/ primary chronic hearing loss #
B.	**Individual central sensitivity syndrome**
1.	Complex regional pain syndrome

*See Table 3 for criteria for classification in this category.

** An individual central sensitivity syndrome, e.g. complex regional pain syndrome, has not been reported to be associated with any of the diseases of the CSS family as listed under A. Also, unlike CSS conditions, CRPS patients may have prominent physical signs (see text).

Provisional classification. Evidence for CS is very likely but yet to be confirmed in these conditions, although an association with another member of the CSS family has been reported.

family are shown in Table **3**. Note that CRPS is an individual primary central sensitivity syndrome that is not a member of the CSS family (Table **2**) since to the author's knowledge, no association with a member of the CSS family (criterion 2, Table **3**) has been reported.

The criteria for the CSS family are meant for classification in research. It is impractical to use them in clinical practice at this time both because of a general unavailability of human pain laboratory and the absence of satisfactory normative data to which augmented response in CS can be compared with. There is an immense individual variability in CS based on gender and age, types of stimulation (pressure, temperature, etc.), types of tissue (skin, muscle, mucosa) and presence of psychobiological factors. For example, nociceptive flexion reflex (NFR) [1] is not influenced by psychobiological elements [31].

A group of pain experts from seven countries recently suggested criteria for CS, however, for clinical use [96]. The paper mentions "increased responsiveness to a variety of stimuli," but it does not specify how the "increased" response will be determined [96]. Quantitative sensory testing (QST) using mechanical and thermal stimuli has been recommended, however, for assessment of neuropathic pain, particularly in SFN that cannot be assessed by conventional electrophysiology [97]. This review [97] also reports test-retest reliability and validity of QST.

Since the introduction of the term 'central sensitivity syndromes,' first in 2000 [28], it has been widely used [1, 3-7, 99-114]. In fact, in a well-designed study, Mayer, *et al.* developed and validated Central Sensitization Inventory (CSI) with high reliability and validity [104] based on the construct of CSS [1]. CSI was subsequently found to be useful in diagnosing a CSS condition in the clinic [105].

Table **2** shows proposed current members of CSS. The number of CSS conditions is most likely to increase substantially by future research. The discussion in this section will be limited to the evidence of CS in selected CSS diseases. An updated evidence of CS in FMS [87], painful bladder syndrome (PBS)/ interstitial cystitis (IC), endometriosis, primary dysmenorrhea and vulvodynia [107], myofascial TMD [109], IBS [112], TTH [113], migraine [114], RLS [115] and CI/ multiple chemical sensitivity [116] has been provided by different authors in the thematic issues of CRR.

Evidence of CS in PTSD is absent or inconsistent [92, 117]. Absence of CS in this disorder in several studies [92, 117] has been attributed to emotional numbing from a highly unpleasant past memory [92].

I have added a few new members (Table **2**) compared with those listed earlier [1]. These are primary (so-called functional) dyspepsia, primary chronic neck pain, primary chronic LBP, endometriosis, chronic prostatitis, vulvodynia and burning mouth syndrome.

Some regional pain syndromes (neck pain, LBP, myofascial pain syndrome) may morph into generalized pain [118]. Repetitive strain injury of the upper extremity, usually related to occupation [119] is an important common regional pain syndrome that is likely to be due to CS. Unfortunately this condition has not received much attention, probably because of the compensation politics. These regional pain conditions belong to the spectrum of FMS.

The symptoms in chronic prostatitis are similar to those with PBS/IC, e.g. increased frequency of urination, dysuria and nocturia in the absence of infection or benign prostatic hyperplasia. Acute attacks may be agonizing with intense dysuria. There is evidence of CS in chronic prostatitis [120, 121]. National Institute of Health Chronic Prostatitis Symptoms Index (NIH-CPSI) [108] provides the spectrum of symptoms that need further studies.

There is good evidence for CS in primary chronic neck pain, including whiplash associated disorder [1,122], and for primary LBP [123].

Primary dyspepsia (PD) may be considered part of an IBS spectrum. Patients present with features of dyspepsia without an underlying pathology (e.g. peptic ulcer) and without colon symptoms. There is evidence of CS in primary dyspepsia [1, 124-126]. PD is associated with other members of the CSS family [125].

Primary burning mouth syndrome (BMS) is characterized by bothersome burning in the tongue (glossodynia) and the oral mucosa without an underlying cause, e.g. infection, mouth ulcer and nutritional deficiency [127-129]. Other symptoms are numbness and altered taste (dysgeusia). There is evidence for both peripheral and central sensitization with

Table 3. Proposed classification criteria for a primary central sensitivity syndrome as a member of the central sensitivity syndromes (CSS) family for research purpose.

All the following three criteria should be met:
1. Presence of central sensitization (CS)*
2. Association with another member of the CSS family based on a study with a matched control group or well established age and gender matched population control
3. Absence of an underlying disease that may cause CS (see Table 1)**

*CS may be determined by (a) quantitative sensory testing (QST); (b) other tests to determine the CNS hypersensitivity, e.g. the vagal system at the level of nucleus tractus solitarius in the case of primary chronic cough. QST-all available standardized tests in all tissues (skin, muscle, mucosa) should be undertaken with matched healthy painfree controls to determine if augmented response (compared with normal controls) is present or absent in a given condition, using pressure, pinprick, cold, heat, vibration, electricity, ischemia and chemical (capsaicin, hypertonic saline) stimuli using both ascending and random paradigms. Patients should be tested for allodynia (using cotton swab, brush, Von Frey filaments), temporal summation, conditioned pain modulation and nociceptive flexion reflex (see reference 1). To qualify for CS, hyperresponsiveness should be present at sites distant from the site of pain symptom (in localized conditions, e.g. neck pain) in nonsegmental distribution.

** Peripheral pathology, e.g. small fiber neuropathy or inflammation in the absence of an underlying disease (e.g. diabetes mellitus or arthritis) is not an exclusion. Note that complex regional pain syndrome (Table **2**) is an individual central sensitivity syndrome and not part of the CSS family since criterion 2 is not currently met. Also note that the previous 2007 criteria [1] of an absence of structural pathology is now omitted in view of well documented peripheral pathology being present among the members of CSS family (see text). Instead, these conditions are regarded primary without an underlying cause, e.g. OA and RA (see Table **2**).

hypoalgesia, hyperalgesia and allodynia [128]. Particularly convincing is the presence of SFN with hypesthesia and lower density of epithelial and subepithelial nerve fibers in the tongue compared with controls [129], similar to the findings in FMS [130]. Heat pain detection threshold was reduced on the wrist in patients with BMS [131]. BMS is associated with FMS and TMD [132, 133].

Primary (idiopathic) chronic cough (PCC) in the absence of an underlying cause is quite likely to be due to CS [134], although data are lacking. Patients are mostly female and complain of bothering persistent cough. Analogous to hyperalgesia in peripheral nervous system, hypertussia is provoked by much lower concentration of a tussive agent, e.g. inhaled capsaicin, as compared with normal controls [135]. The afferent A delta and C fibers of airways are provided by the vagal nerve that project into caudal nucleus tractus solitarius (nTS) in the medulla that mediate cough [134]. PCC is significantly associated with IBS [136].

Primary chronic tinnitus (PCT) is characterized by ringing in the ear and perception of a sound, e.g. a noise or a tone, in the absence of external sound source, as has been reviewed [137]. It is accompanied with hearing loss in 90%. Thus, two primary otological conditions may be categorized together. PCT persists or gets worse after transection of the eighth cranial nerve that abolishes cochlear input to the brain, reminiscent of CS where pain at distant sites continues even after the peripheral input is eliminated (e.g. replacement of an inflamed joint). Tinnitus is likely mediated by a central (brain) mechanism irrespective of the degree of peripheral damage that might have initiated it [137]. Hearing loss has been reported in FMS [138, 139]. In an uncontrolled study, 16.7% of patients with FMS reported having tinnitus and 12.5% had hearing loss [139].

Isolated pain without a local cause has been described in tooth or oral gum (odontalgia) [140], eyeball (ophthalmodynia) [141] and nose (rhinalgia) [141]. These are also likely to be due to CS. QST studies suggested CS in odontalgia [140]. With regards to pain in the eye ball, it is interesting that we reported such pain in a fibromyalgia patient in 1981 [142]. At that time it was quite bewildering.

Central sensitivity syndrome as an individual condition separate from CSS. I propose CRPS belongs to a different category (Table **2**). It is not part of the CSS family, since no association with other members of CSS has been reported to my knowledge. Several subgroups in CRPS have been described, one of these has clear evidence of CS with generalized hyperalgesia [143, 144]. Phenotypically, patients with CRPS are very different from those with CSS—they have vasomotor changes in the extremities with objective skin discoloration, warmth or cold and marked objective swelling. Patients also have impaired motor function having dystonic features, e.g. persistent flexion postures of the fingers and wrist, toes and the legs, as well as tremor. These features have been attributed to neurogenic inflammation, mediated by CGRP and substance P [143, 144]. One of the striking features of CRPS is disturbance of body representation [144]. The affected side, for example, seems too large with a distorted position sense. Given identifiable structural pathology, including inflammation, objective physical signs (e.g. skin discoloration, swelling and dystonia) and genetic predisposition [143], CRPS may be classified as a disease in its own right (rather than a syndrome). Thus it may alternatively be classified under B 2 (secondary to well defined pathology/disease, etc.) in Table **1**. Future research may provide a clearer picture.

Peripheral Pathology and Immunology in CSS

The CNS model for FMS, first suggested in 1992, included peripheral contribution to the central pain [145]. In recent years, it has become clear that CSS patients have neuroimmunopathological and histopathological changes with inflammation in peripheral tissues (see below) that may contribute to peripheral sensitization and priming of afferents leading to CS [9].

For a long time, numbness, tingling and burning in the extremities among patients with FMS were thought to be "psychological". In recent years several controlled and blinded studies have shown large fiber [146] and small fiber [130, 147-150] neuropathy in FMS, as has one uncontrolled study [151]. An underlying cause of SFN, e.g. diabetes mellitus was excluded. Physical examination may show both hypesthesia and hyperthesia [130], similar to BMS. SFN was diagnosed by decreased epidermal nerve fiber density (ENFD) by skin biopsy in five studies [130, 147-149, 151] and by confocal corneal biomicroscopy in the other [150]. There was an inverse relationship between ENFD and serum IL-2R [130]. Additionally, IL- 1 beta, IL-6 and TNF alpha were found in skin biopsy of patients with FMS vs none among controls [152]. SFN in FMS may thus be immune mediated [130]. SFN was also found in the trigeminal nerve in BMS by tongue biopsy as stated earlier and in RLS by skin biopsy [153].

A number of studies in FMS have found cytokine abnormalities [4, 154]. Reviewing 25 studies with 1255 FMS patients and 800 healthy controls, Uceyler, *et al.* concluded that serum IL-1 ra, IL-6 and IL-8 cytokines are elevated in FMS [154]. Serum IL-6 and IL-8 were elevated in IBS [155]. IL-6 is also elevated in PBS (interstitial cystitis) with increased response of IL-1beta to stimulation by TLR-2 [156].

A large number of controlled studies have consistently shown histological changes in the bladder epithelium in IC with denudation, ulceration and cellular infiltration with mastocytes as well as increased expression of neurostimulatory molecules, e.g. NGF, bradykinin receptor and TRPV1 [157]. Intestinal biopsy in IBS have shown low grade inflammation with increased mucosal mast cells with apposition of nerve fibers containing substance P and CGRP [158, 159].

Vulvodynia has been well-reviewed [107, 160]. Although it has been classified as localized provoked vulvodynia (LPV) and generalized (GVD) varieties, they are likely to be a continuum [160]. Recurrent history of vulvovaginal candidiasis is common. Inflammatory nature of the vulvar vestibule has been well recognized with infiltration of lymphocytes and mast cells [161]. Foster DC, *et al.* found enhanced production of IL-6 and PGE_2 by fibroblasts in response to stimuli by live yeasts in the vestibular area as compared with external vulvar fibroblast [162]. Local vestibular inflammation explains peripheral, and potentially central, sensitization [163].

Thus, peripheral sensitization from sensitized peripheral tissue secondary to physical trauma and microtrauma in the muscles, SFN in the extremities or the tongue and inflammation in the bladder and the vulvar vestibule leads to CS. There is a great deal of variability, however, between individuals and diseases; some have considerable peripheral input and others apparently have none. Morphine, may cause CS via a direct central mechanism. A general schema showing various factors contributing to CS and CSS is shown in (Fig. **1**).

PROGRESS IN NEUROIMAGING IN CSS AND CHRONIC PAIN

The understanding of CS has been significantly advanced by a remarkable progress in brain neuroimaging by different techniques [7, 164-172]. Such techniques have provided a much needed objective neuronal correlate of subjective pain, so that one can literarily "see" pain. Response to nociceptive stimulation in human beings could be directly visualized. Then came the phenomenal discovery of observing brain activities in resting state, first reported by Bharat Biswal in 1995 [167]. The resting state neuronal activities have since been described in chronic pain by various methods of functional MRI [168].

Remarkably, structural changes, including microscopic morphology in the white matter and volume changes in the gray matter are now discernible in CSS conditions [7, 165, 168], making distinction between the so-called "organic" (structural) and "functional" (neurochemical-structural) pathologies difficult.

White matter comprises of the extensive network of myelinated neurons that connect different distant brain regions. Abnormal intrinsic brain connectivity can be visualized by resting-state FMRI and neural correlates of chronic pain assessed. The intensity of spontaneous pain in FMS was correlated with greater intrinsic brain connectivity in multiple brain networks [169]. Neuroimaging has also made it possible to measure neurotransmitters in CSS [7], e.g. glutamate, which is increased in the brain in several CSS conditions [7], including IBS [170].

Pain network areas are activated on a painful stimulation in CSS. The sensory processing areas include S1,S2, thalamus, posterior insula, ACC and dorsolateral prefrontal cortex (PFC) [7, 168]. Some of these areas (e.g. ACC, PFC and thalamus) overlap in several members of the CSS family (FMS, IBS, TMD, vulvodynia) providing an objective "neuroimaging signature" of CS in CSS [7]. The affective processing areas involve anterior insula and ACC [168]. PFC may be related to cognitive aspects of pain [7]. Similarly, several common areas of gray matter atrophy (ACC and thalamus) are seen in FMS, IBS and TMD, again suggesting a common central mechanism among CSS members [7] and in chronic pain in general.

It seems gray matter atrophy is both a cause and consequence of chronic pain, and the same may be said of CS. One study followed patients with subacute LBP for a year [171]. Compared with the improved group, the persistent pain group showed a decrease in gray matter volume in bilateral striatum. Further, greater functional connectivity of nucleus accumbens with PFC at the beginning predicted per-

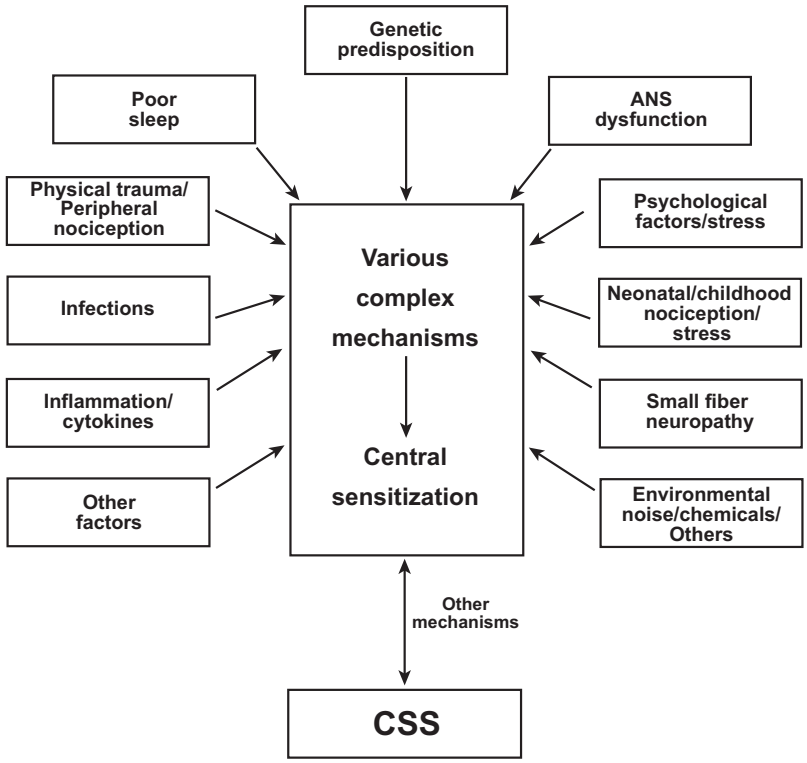

Fig. (1). Different factors, both peripheral and central, contribute to the complex pathophysiology of central sensitization (CS) and sensitivity syndromes (CSS); see text. "Other factors" include drugs, e.g. opioids. The relationship between CSS and CS is likely to be bidirectional; chronicity may enhance existing CS. ANS-autonomic nervous system.

sistence of pain, implying that the corticostrial circuitry is causally involved in chronification of pain [171]. A longitudinal study of experimental neuropathic pain in rats showed decreased frontal lobe volume several months after the injury suggesting a causal link [172].

Considering the comorbidity between major depressive disorder (MDD) and pain, it is not surprising that there are overlapping areas of brain changes by neuroimaging between two conditions but with important differences. In MDD, increased activity has been found in ventromedial PFC, ACC and amygdala. However, the activity in insula is *decreased* and there is decreased hippocampal volume [173]. As expected, somatosensory areas are not involved in MDD.

NOSOLOGY, BIOLOGY, PSYCHOBIOLOGY, AND PARALOGY

"Functional" vs. "organic." Names and naming are important matters. Often names conjure an image, consciously or subconsciously, that is positive, negative or neutral. With regards to CSS conditions, they are commonly referred as "functional syndromes" different from "organic diseases" as have been discussed [98].

It would seem that the terms "organic" vs "functional" were coined at a time when mental symptoms were deemed imaginary, not originating in an organ (hence not organic) and there were no objective signs on physical examination or any abnormal laboratory or X-ray findings to support this opinion. The word functional is sometimes meant to be psychogenic even in its recent use [174].

Currently one can visualize pain-related changes in the brain by neuroimaging in CSS conditions. Physical examination shows both hypesthesia and hyperesthesia in the legs in FMS [130]. Skin biopsy shows SFN. There is exaggerated NFR which is a fully objective test that does not require any patient response [1] and it is not influenced by psychobiological factors [31]. Abnormal neurotransmitters can be measured in FMS in cerebrospinal fluid [175] and in the brain [7, 170].

I agree with Russell and Larson [175] that it is no longer accurate to say FMS is a "poorly understood" or "mysterious" disease and that its cause is unknown (although the causes of CSS are incompletely understood).

The term "functional" (vs. "organic") is nonsensical. Functional relates to physiology or normal. In CSS conditions, the neurochemical pathology is in the spinal cord and the brain, and both are organs!

I suggest the change of the terms "functional" and "organic" to 'diseases with neurochemical-structural pathology' (DNP) and 'diseases with structural pathology' (DSP), respectively. These terms may seem 'mouthful' or 'earful,' but they are truthful! Similarly, psychiatry should be labeled as neuropsychiatry. These are all parts of the spectrum of medicine. At St. Louis University, USA, Psychiatry belongs to one single department of Neurology and Psychiatry [neuroandpsych.slu.edu].

Psychobiology vs biology. Some authors use the word 'biology' to mean "organic" disease [176]. I suggest the term 'psychobiology' instead of 'psychology.' Psychobiology is biology based on genetics and neurochemistry, and genetics is as biological as it gets; there is no life without DNA! I have previously suggested abolition of the illness-disease dichotomy [98] for the same reason, particularly because illness has a connotation that patients' symptoms are psychological and not as important as a disease like RA (but the same patient can have both!).

Cutting the "functional"- "organic" dichotomy. The mind-body or mental-physical dichotomy is irrational and ancient (a close cousin of mental-physical is "functional"-"organic") and harmful. An author in DSM-IV astutely said "…the term mental disorder unfortunately implies a distinction between "mental" disorders and "physical" disorders that is a reductionist anachronism of mind/body dualism. A compelling literature documents that that there is much "physical" in "mental" disorders and much "mental" in "physical" disorders." [179]. In keeping with this statement, many patients with structural pathology also have neurochemical pathology (e.g. CS) (Table **1**). Similar to the role of proinflammatory cytokines in RA, these cytokines are also elevated in FMS [4, 154], IBS [155], IC/PBS [156] and depression [177], blurring the distinction between the DNP and DSP disorders. Others also have called for an abandonment of "functional"- "organic" dichotomy [180]. Ellen Langer, a well-known Harvard psychologist, states that mind-body dualism is dangerous and has serious consequences [181].

"*Medically unexplained."* Another dubious terminology that has crept up in the literature is "medically unexplained symptoms" [98]. This is another meaningless distinction between psychobiology and non-psychological biology. Both belong to the science of medicine.

Blaming the patients. Terms like somatization, somatizers and catastrophizing have the implication that somehow the patients are actively and willfully involved in producing their symptoms! The Greek word soma simply means body and symptoms of *all* diseases belong to the body! But the term somatization has come to mean many symptoms that cannot be explained by "pathological findings" as originally defined by Lapowski in 1988 [182]. Much progress has been made in CSS conditions since. Patients with a connective tissue disease also have many symptoms related to multiple organs, but some authors use the words 'somatic' and 'somatization' preferentially for diseases like fibromyalgia [183]. Since symptoms in CSS are explicable by their pathophysiology, Lapowski's original definition does not apply to CSS.

Several authors have realized the inappropriateness of using terms like somatization and somatizers. Thus, terms like multiple physical symptoms [184] and multisite symptoms [185] have been suggested. Another phrase that may be meaningful is "multisystem symptoms." I suggest avoiding the term 'somatic' in the context of CSS since it implies "all psychological." We should avoid unnecessary psycholization of CSS conditions. Such psycholization causes physician-patient conflict [186]. 'Catastrophize' may be changed to 'thoughts of catastrophe.'

Selective bias of psycho-centric physicians and other health care providers towards CSS disorders. Imagine a physician telling a patient with FMS: "You have a condition

that cannot be explained medically, and actually you are a somatizer." Some authors seem to be persistent in psycholizing CSS disorders like FMS with remarks such as "psychological factors are an integral part of the syndrome" [187]. Psychological factors are integral to human living and are present in *all* diseases in varying degrees. Psychobiological factors are present only in a subgroup of FMS patients [188, 189] with a great deal of individual variability. "Catastrophizing" (catastrophic thoughts), are also present in DSP, e.g. RA and spondylitis [190].

The word 'distress' is frequently used particularly in the context of CSS disorders [183]. Such psycholization of patient symptoms is unwarranted and unnecessary. Some patients with any disease, e.g. Sjogren's syndrome [191] feel distressed also. It is unfortunate that "Bodily distress syndrome" was coined particularly with CSS disorders in mind [192].

"Functional"- "organic" dichotomy and person-centered care. There is a great deal of individual variation among chronic pain patients [188, 189], calling for person-centered care [193]. "Group thinking" based on pathology, e.g. RA or FMS is not conducive to optimal personalized care. An individual may have both. The degree of distress is variable in any disease hence the focus should be on an individual and not on a disease. As Engel pointed out, biopsychosocial model also applies to acute diseases, e.g. acute myocardial infarction [194]. An appropriate treatment should address peripheral and central sensitization as well as the psychobiological factors.

One must not take the role of psychobiology in diseases lightly. Patients with thoughts of catastrophe irrespective of diagnosis have worse outcome [195] and need focus on psychobiological treatment that is helpful [196, 197]. Catastrophic thoughts are associated with pain augmentation as evidenced by increased activity in several brain areas including claustrum, dorsolateral PFC and ACC [198].

Brain imaging is increasingly being used to evaluate efficacy of therapy, both pharmacological and non-pharmacological, and identify subgroups that may benefit from such therapy [199, 200].

CONCLUSION

CS is an important new clinical concept that has helped to better explain the mechanisms of pain in common diseases, e.g. FMS, IBS, RA and OA. CS binds CSS members, e.g. FMS, IBS and myofascial TMD. CS may not be the only mechanisms for these conditions. Fatigue, for example, may have a different mechanism. CS itself has many mechanisms, e.g. TS and CPM that have bearing on subgrouping, management and future drug development.

CS may be caused by or associated with a number of diseases that are shown in Table **1**. This is important since treatment of OA or RA, for example, with focus on peripheral pathology alone will not provide satisfactory treatment if they also have CS that needs treatment of the CNS component with centrally acting medications and non-pharmacological modalities. On the other hand, peripheral component of a CSS condition needs appropriate treatment as has been discussed. New drugs are being tested for SFN, the treatment of which is unsatisfactory.

There has been remarkable progress in neuroimaging in recent years, so that changes in both the grey and white matters of the brain can be visualized in chronic diseases helping a better understanding of disease mechanisms and more targeted treatment.

With regards to nosology, I have suggested abandoning the "functional"- "organic" divide since many diseases have both and this dichotomy has caused physician-patient conflict with detriment to patient care. With regards to management, one should focus on the person (rather than the group diagnosis). Some terms like somatization, somatizers and catastrophizing have a connotation of blaming the patients and should be replaced with neutral names as suggested. Person/patient centered management is important and involves both nonpharmacological and pharmacological approach that will vary according to an individual patient's needs.

FUTURE DIRECTIONS

I suggest the following: (1) Found an international society of central sensitization (ISCS) with its own journal related to CS; from my literature search, such an organization or journal does not seem to currently exist. ISCS may have two broad sections: basic science and clinical science; (2) By ISCS initiative, cull an international group of experts to formulate a uniform classification criteria for CS that can be used for both research and clinical settings; (3) Considering immense suffering from chronic pain, devote more effort and funding for both basic science (including genetics, epigenetics, neuroendocrine, neurosensory, neurophysiology and immunology areas) and clinical (including psychobiological and epidemiologic) research. Epidemiologic studies of asymptomatic individuals with follow up will help determine cause-effect relationships of CS and better interpretation of brain imaging findings; (4) Focus on developing new therapeutic molecules based on increasing knowledge in CS; (5) Develop reliable and objective biomarkers for diseases and specific mechanisms; (6) Emphasize subgroups and person/patient-centered approach for treatment employing biopsychosocial model.

LIST OF ABBREVIATIONS

ACC	=	anterior cingulate cortex
BDNF	=	brain-derived nerve growth factor
BMS	=	Burning mouth syndrome
CBT	=	cognitive behavioral therapy
CES	=	cognitive emotional sensitization
CFS	=	chronic fatigue syndrome
CGRP	=	calcitonin gene-related peptide
CI	=	chemical intolerance
CPP	=	chronic pelvic pain
CRPS	=	complex regional pain syndrome
CNS	=	central nervous system

CPM	=	conditioned pain modulation
CS	=	central sensitization
CSS	=	central sensitivity syndromes
DNP	=	disease with neurochemical-structural pathology
DSP	=	disease with structural pathology
ENFD	=	epidermal nerve fiber density
FMS	=	fibromyalgia syndrome
IBS	=	irritable bowel syndrome
IASP	=	International Association for Study of Pain
IC	=	interstitial cystitis
LBP	=	low back pain
MPS	=	myofascial pain syndrome
NFS	=	nociceptive flexion reflex
NGF	=	Nerve growth factor
NMDA	=	N-methyl-D-aspartate
NSAID	=	nonsteroidal anti-inflammatory drug
nTS	=	nucleus tractus solitaris
OA	=	osteoarthritis
PAG	=	Periaqueductal gray
PBS	=	painful bladder syndrome
PCC	=	primary chronic cough
PCM	=	person-centered management
PCT	=	primary chronic tinnitus
PD	=	primary dyspepsia
PFC	=	prefrontal cortex
QST	=	quantitative sensory testing
RA	=	rheumatoid arthritis
RLS	=	restless legs syndrome
SFN	=	small fiber neuropathy
SP	=	substance P
TMD	=	temporomandibular disorder
TS	=	temporal summation

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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