

Epidemiology

Applying Modern Pain Neuroscience in Clinical Practice: Criteria for the Classification of Central Sensitization Pain

Jo Nijs, PhD^{1,2}, Rafael Torres-Cueco, MSc³, C. Paul van Wilgen, PhD⁴, Enrique Lluch Gírbés, MSc³, Filip Struyf, PhD^{1,5}, Nathalie Roussel, PhD^{1,5}, Jessica Van Oosterwijck, PhD^{1,6}, Liesbeth Daenen, PhD^{1,7}, Kevin Kuppens, MSc^{1,5,7}, Luc Vanderweeën, MSc^{1,8}, Linda Hermans, MSc⁶, David Beckwée, MSc¹, Lennard Voogt, PhD^{1,9}, Jacqui Clark, MSc¹⁰, Niamh Moloney, PhD^{1,11}, and Mira Meeus, PhD^{6,7}

From: ¹Pain in Motion Research Group, Departments of Human Physiology and Physiotherapy, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Belgium; ²Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Belgium; ³Department of Rehabilitation, University of Valencia, Spain; ⁴Transcare, Transdisciplinary Painmanagement Centre, Groningen, The Netherlands; ⁵Rehabilitation Sciences and Physiotherapy, Faculty of Medicine, Antwerp University, Antwerp, Belgium; ⁶Department of Rehabilitation Sciences, Ghent University, Ghent, Belgium; ⁷Department of Neurology, Faculty of Medicine, Antwerp University, Antwerp, Belgium; ⁸Private Practice for Spinal Manual Therapy, Schepdaal-Dilbeek, Belgium; ⁹Master Program in Manual Physiotherapy, Rotterdam University College, The Netherlands; ¹⁰Faculty of Health, Psychology and Social Care, Manchester Metropolitan University, United Kingdom; ¹¹Discipline of Physiotherapy, Faculty of Health Sciences, The University of Sydney, Australia

Address Correspondence:
Jo Nijs, PhD
Vrije Universiteit Brussel, Building F-Kine
Laarbeeklaan 103, BE-1090
Brussels, Belgium
E-mail: Jo.Nijs@vub.ac.be

Disclaimer, Conflicts of Interest on P. 455.

Manuscript received: 02-22-2014
Revised manuscript received: 05-05-2014
Accepted for publication: 06-10-2014

Free full manuscript:
www.painphysicianjournal.com

Background: The awareness is growing that central sensitization is of prime importance for the assessment and management of chronic pain, but its classification is challenging clinically since no gold standard method of assessment exists.

Objectives: Designing the first set of classification criteria for the classification of central sensitization pain.

Methods: A body of evidence from original research papers was used by 18 pain experts from 7 different countries to design the first classification criteria for central sensitization pain.

Results: It is proposed that the classification of central sensitization pain entails 2 major steps: the exclusion of neuropathic pain and the differential classification of nociceptive versus central sensitization pain. For the former, the International Association for the Study of Pain diagnostic criteria are available for diagnosing or excluding neuropathic pain. For the latter, clinicians are advised to screen their patients for 3 major classification criteria, and use them to complete the classification algorithm for each individual patient with chronic pain. The first and obligatory criterion entails disproportionate pain, implying that the severity of pain and related reported or perceived disability are disproportionate to the nature and extent of injury or pathology (i.e., tissue damage or structural impairments). The 2 remaining criteria are 1) the presence of diffuse pain distribution, allodynia, and hyperalgesia; and 2) hypersensitivity of senses unrelated to the musculoskeletal system (defined as a score of at least 40 on the Central Sensitization Inventory).

Limitations: Although based on direct and indirect research findings, the classification algorithm requires experimental testing in future studies.

Conclusion: Clinicians can use the proposed classification algorithm for differentiating neuropathic, nociceptive, and central sensitization pain.

Key words: Chronic pain, diagnosis, hypersensitivity, classification, neuropathic pain

Pain Physician 2014; 17:447-457

Many chronic pain patients, including those with persisting neck pain (1-4), pelvic pain (5,6), low back pain (7-9), fibromyalgia (8,10,11), subacromial impingement syndrome (12),

chronic fatigue syndrome (13), tension-type headache (14), migraine (15), osteoarthritis (8,16,17), rheumatoid arthritis (18), tennis elbow (19,20), nonspecific arm pain (21), and patella tendinopathy (22) show features

suggestive of central sensitization (CS), a process characterized by generalized hypersensitivity of the somatosensory system (23-25). According to Woolf (26), CS is "operationally defined as an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity." These studies provide evidence supporting the presence of CS in patients with chronic pain through observational brain imaging studies, psychophysical testing with various stimuli, and cerebral metabolism studies (5,7,8,12-16,19,20,27).

CS reflects increased activity of pain facilitation pathways (11,27) and malfunctioning of descending pain inhibitory pathways which result in dysfunctional endogenous analgesic control (13). In addition, the pain neuromatrix is likely to be overactive in patients with CS: Increased activity is present in brain areas known to be involved in acute pain sensations and emotional representations like the insula, anterior cingulate cortex, and the prefrontal cortex, but not in the primary or secondary somatosensory cortex (28). An overactive pain neuromatrix entails brain activity in regions not involved in acute pain sensations including various brain stem nuclei, dorsolateral frontal cortex, and the parietal associated cortex (28). Research findings also suggest a specific role of the brainstem for the maintenance of CS in humans (29). Furthermore, long-term potentiation of neuronal synapses in the anterior cingulate cortex (30), nucleus accumbens, insula, and the sensorimotor cortex, as well as decreased gamma-aminobutyric acid-neurotransmission (31) represent 2 potential mechanisms contributing to the overactive pain neuromatrix.

As mentioned, the concept of CS has been studied extensively in different patient cohorts (1,2-5,8,12-15,18,19,32), showing that CS may modulate the development of pain (e.g., in fibromyalgia) and/or the transition from acute to chronic pain (e.g., whiplash associated disorder) (4,33) in patients where an obvious source of nociception is absent. CS in these patient groups can also mediate treatment responses (2,20) thus inviting clinicians to consider targeting the processes underlying CS when treating patients with chronic pain (24,34). A limited body of evidence suggests that some of the mechanisms underlying CS may be responsive to clinical interventions. For example, there is some evidence to suggest that effective treatment for chronic low back pain may reverse abnormal brain function (35,36), and that biopsychosocially-driven rehabilitation may reduce central nervous system hyperexcitability (37) and increase prefrontal cortical volume (38)

in patients with chronic pain although larger trials are required to further substantiate these findings. Finally, the clinical importance of CS is supported by findings in chronic low back pain patients. Compared to those classified as having peripheral neuropathic pain and nociceptive pain, patients with CS reported more severe pain, poorer general health-related quality of life, and greater levels of back pain-related disability, depression, and anxiety (39).

In some patient populations, CS may be the characteristic feature of the disorder, as is the case with chronic whiplash, fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome (25). Not all chronic pain patients have CS, but it may underlie sub-groups of patients with chronic low back pain, whiplash, osteoarthritis, rheumatoid arthritis, tennis elbow pain, shoulder pain, and headache (8,12,14-18,25,40,41). The reasons for this are unknown, but may reflect a genetic predisposition and the influence of other biopsychosocial factors. At the group level, these populations may be characterized by CS, but at the individual level definitely not all patients show evidence of CS. Rather, a subgroup of these populations is characterized by CS. If present, CS may dominate the clinical picture, modulate the transition to chronicity (4,33), and mediate treatment responses (2,20). Therefore, it may be considered important for clinicians to be able to identify or diagnose CS in patient populations presenting for treatment.

While patients with chronic pain are more likely to present with CS, CS may not be limited to chronic pain states. For example, in patients with whiplash associated disorders, abnormal sensory processing may appear quite rapidly (< 7 days) after the initial whiplash trauma, and once present, it has an important predictive ability for the development of chronicity (4,42). Hence, it is important for clinicians to rapidly identify CS in patients with (sub)acute pain for the early identification of the risk for chronicity.

Although awareness is growing that CS may be of prime importance in the development, persistence, and management of chronic pain, its classification is challenging clinically since no gold standard method of assessment exists. In recent years, 2 questionnaires have been developed for the screening of CS, the Pain Sensitivity Questionnaire (43) and the Central Sensitization Inventory (44,45). These questionnaires assess aspects of CS but the inclusion of physical assessment measures and clinical judgments by health care professionals also offer greater potential for the classification

of CS. Guidelines for the recognition of CS in patients with musculoskeletal pain have been proposed (25), and although helpful, they are unable to guide clinicians towards clear-cut classification decisions in clinical practice. Therefore, a body of evidence from original research papers was used by 18 pain experts from 7 different countries to design the first classification criteria for CS pain. Here we propose for the first time a set of classification criteria for CS pain as an entity relatively distinct from other mechanisms-based classifications of pain such as neuropathic and nociceptive pain.

Excluding or Diagnosing Neuropathic Pain as the First Important Step

It is proposed that the classification of CS pain entails 2 major steps: the exclusion of neuropathic pain and the differential classification of nociceptive versus CS pain.

Neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” (46). Neuropathic pain can be both peripheral (i.e., located in a nerve, dorsal root ganglion, or plexus) and central (located in the brain or spinal cord). Neuropathic pain is characterized by sensitization as well; peripheral and central (segmentally related) pain pathways are hyperexcitable in patients with neuropathic pain (47,48). However, here we focus on the classification of non-neuropathic CS pain, implying that exclusion of neuropathic pain is required as the first step. Indeed, typical CS conditions like fibromyalgia, or any other chronic pain condition not due to a lesion or disease of the somatosensory system, do not satisfy the criteria for the classification of neuropathic

pain. Likewise, some patients with chronic low back pain, tennis elbow, or osteoarthritis may show features of CS, but do not fit into the diagnostic criteria for neuropathic pain.

For a detailed description of the diagnostic criteria and clinical diagnosis of neuropathic pain, the readers are referred to the relevant international consensus documents (46,49,50). The main criteria for differentiating between neuropathic and non-neuropathic CS pain are presented in Table 1.

For the purpose of the present paper, it is important to highlight the issue of sensory dysfunction in neuropathic versus non-neuropathic CS pain. Sensory testing is of prime importance for the diagnosis of neuropathic pain (46,49). This includes testing of the function of sensory fibers with simple tools (e.g., a tuning fork for vibration, a soft brush for touch, and cold/warm objects for temperature), which typically assess the relationship between the stimulus and the perceived sensation (49). Several options arise here, all suggestive of neuropathic pain: hyperesthesia, hypoesthesia, hyperalgesia, hypoalgesia, allodynia, paraesthesia, dysesthesia, after sensations, etc. Again, the location of the sensory dysfunction is crucial for the differential classification between neuropathic and non-neuropathic CS pain. While in neuropathic pain the location of the sensory dysfunction should be neuroanatomically logical, in non-neuropathic CS pain it should be spread in nonsegmentally related areas of the body. In fact, clinical examination in non-neuropathic CS pain typically reveals increased sensitivity at sites segmentally unrelated to the primary source of nociception (25). Findings of numerous areas of hyperalgesia at sites

Table 1. *Criteria for the differential classification between neuropathic (46, 49,50) and non-neuropathic central sensitization (CS) pain.*

Neuropathic pain	Non-neuropathic CS pain
History of a lesion or disease of the nervous system	No history of a lesion or disease of the nervous system
Evidence from diagnostic investigations to reveal an abnormality of the nervous system, or post-traumatic/postsurgical damage to the nervous system	No evidence from diagnostic investigations, or damage to the nervous system
Often related to an established medical cause like cancer, stroke, diabetes, herpes, or neurodegenerative disease	No medical cause for the pain established
Pain is neuroanatomically logical	Pain is neuroanatomically illogical, i.e., located at sites segmentally unrelated to the primary source of nociception
Pain is often described as burning, shooting, or pricking	Pain is not described as burning, shooting, or pricking, but most often as vague and dull
Location of the sensory dysfunction is neuroanatomically logical	Location of the sensory dysfunction is neuroanatomically illogical, i.e., numerous areas of hyperalgesia at sites outside and remote to the symptomatic site – at segmentally unrelated sites

outside and remote to the symptomatic site, together with a nonsegmental general decrease in pressure pain threshold infers a generalized hyperexcitability of central nociceptive pathways or CS (51).

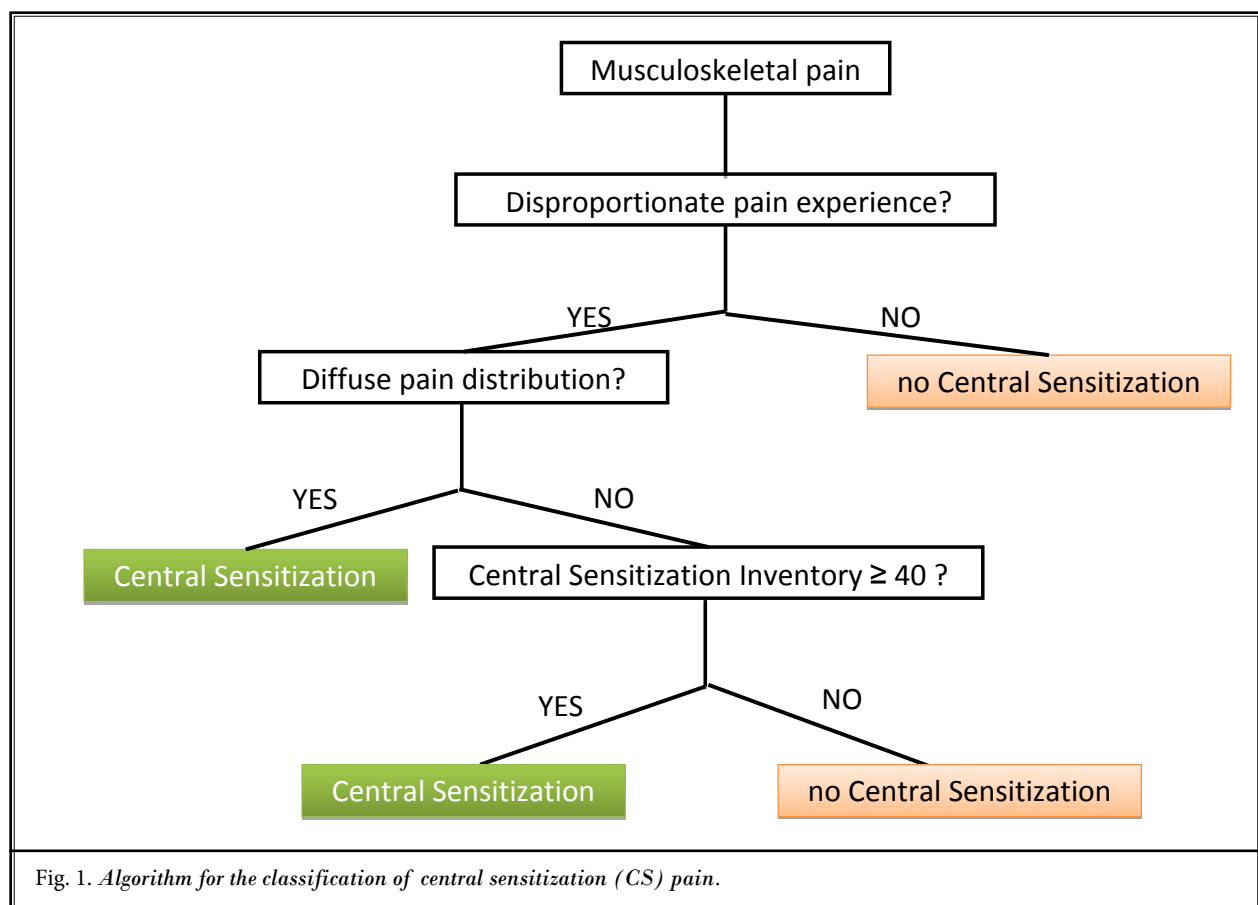
The presence of neuropathic pain does not exclude the possibility of CS or vice versa. In fact, some patients evolve from neuropathic pain with severe but local signs and symptoms, to a widespread pain condition that cannot be explained by neuropathic pain solely. In such cases, CS might account for the evolution to a widespread pain condition.

Classification of Central Sensitization Pain

Once neuropathic pain has been eliminated as a reason, 2 options remain: the (chronic) pain arises from CS (i.e., CS dominates the clinical picture of the patient) or from dominance of peripheral somatic input (i.e., nociceptive pain). Some degree of central pain sensitization in response to acute injury may be considered adaptive in facilitating recovery. Indeed, sensitization of local tissues is a feature of an acute inflammatory

process (e.g., following an acute ankle sprain or muscle injury). When tissue is damaged, the responsiveness of polymodal nociceptive endings is enhanced by various substances released by various sources (such as serotonin released by platelets, bradykinin from the plasma, prostaglandins released by damaged cells, substance *P* released by the primary afferent fibers) (52). This process is called primary hyperalgesia or peripheral sensitization of nociceptors, and is a protective action of the human body to prevent use and consequent further damage of the traumatized and surrounding tissues. Secondary hyperalgesia refers to increased responsiveness of dorsal horn neurons localized in the spinal segment of the primary source of nociception. However, clinicians should aim to differentiate between adaptive peripheral sensitization, for example after an acute inflammatory process, and maladaptive central sensitization.

We propose the following criteria to facilitate this distinction clinically. The criteria should be evaluated together within the classification algorithm (Fig. 1).



These criteria are identifiable from the clinical history and examination. The underlying clinical rationale of these clinical criteria are considered in turn below.

Criterion 1: Pain experience disproportionate to the nature and extent of injury or pathology

This criterion is obligatory for the classification of CS pain. CS is typically characterized by disproportionate pain, implying that the severity of pain and related reported or perceived disability (e.g., restriction and intolerance to daily life activities, to stress, etc.) are disproportionate to the nature and extent of injury or pathology (i.e., tissue damage or structural impairments) (1,4,7,9,12,13-16,19,32,42,53,54). This contradicts nociceptive pain, where the severity of pain and related reported or perceived disability are proportionate to the nature and extent of injury or pathology.

Screening of this first criterion implies that the clinician assesses 1) the patient's amount of injury, pathology, and objective dysfunctions capable of generating nociceptive input, and 2) the self-perceived pain and related disability. Next, the clinician then weighs both in order to answer the following question: Does this patient presents sufficient evidence of injury, pathology, and/or objective dysfunctions for generating nociceptive input capable of causing the self-reported pain and disability? Several answers to this question are possible:

- Yes, this patient presents sufficient evidence of injury, pathology, and/or objective dysfunctions for generating nociceptive input capable of causing the self-reported pain and disability. This would imply that the patient has nociceptive pain, or at least a clinical picture dominated by nociceptive pain (Fig. 1).
- No, this patient presents insufficient evidence of injury, pathology, or objective dysfunctions for generating nociceptive input capable of causing the self-reported pain and disability. This would imply that the patient fulfills this first out of 3 criteria for CS pain; the patient may have CS pain. We proceed with screening of the remaining criteria.
- There is evidence of injury, pathology, or objective dysfunctions for generating nociceptive input capable of causing pain and disability, but not enough for explaining the pain and disability experienced by this patient. Again, this would imply that the patient fulfills this first out of 3 criteria for

CS pain; the patient may have CS pain. We proceed with screening of the remaining criteria.

An example of disproportionate pain may be a patient with chronic neck pain, who suffered an apparently minor injury, with no structural lesions on cervical scans, but a complex clinical picture of various symptoms, including segmentally unrelated pain areas and severe disability. This scenario is typically seen in patients with chronic whiplash associated disorders (grade 1 – 2) (1,3,4,32).

Patients with osteoarthritis typically have (some) tissue damage (i.e., cartilage destruction), yet standard radiological findings show little or no association with pain severity or perceived disability (55). At the same time, mounting evidence supports an important role for CS in patients with osteoarthritis (8,17,55-58).

In addition, there are patient cohorts with severe pain in the absence of any discernible tissue damage or pathology. In this group, nociception is not or has not been present, and yet they continue to have severe pain and related disability. This has been shown consistently in studies of various patient populations, including fibromyalgia (53), chronic fatigue syndrome (13,59), migraine (15), and chronic low back pain (7-9). It is clear that this group complies with this criterion.

The presence of disproportionate pain implies some pain of central pain origin, but does not necessarily reflect CS pain. Therefore, additional criteria should be met before one can consider CS as the dominant mechanism explaining the patient's pain.

Criterion 2: Diffuse pain distribution, allodynia, and hyperalgesia

This criterion addresses patient self-reported pain distribution as identified from the clinical history and/or a body chart (for instance, the Margolis Pain Diagram uses 2 body outlines, front and back, in which patients have to shade the body parts where they felt pain lasting for more than 24 hours in the past 4 weeks (60). At least one of the following, partly overlapping, patterns of pain distribution should be present to fulfill this criterion:

- bilateral pain/mirror pain (i.e., a symmetrical pain pattern);
- pain varying in (anatomical) location/traveling pain, including to anatomical locations unrelated to the presumed source of nociception e.g., hemilateral pain, large pain areas with a nonsegmental (i.e., neuroanatomically illogical) distribution;

- widespread pain (defined as pain located axial, on the left and right side of the body and above and under the waist) (61);
- and/or allodynia/hyperalgesia outside the segmental area of (presumed) primary nociception (3,12,17,19,59).

This overview of patterns of pain distribution is not comprehensive, but it provides a list of frequently occurring patterns considered indicative of CS, as they cannot be explained by a local nociceptive source.

Criterion 2 is mainly screened through questioning, although allodynia/hyperalgesia can be examined on palpation or sensory testing as well (i.e., allodynia to non-noxious mechanical stimuli such as light touch and hyperalgesia to pin prick or heat and cold). Diffuse/non-anatomic areas of pain/tenderness are typically found on palpation (40). Allodynia and/or hyperalgesia outside the segmental area of primary nociception has been used for establishing CS in studies of various chronic pain disorders (including whiplash, epicondylitis, subacromial impingement syndrome, chronic fatigue syndrome, nonspecific arm pain) (3,12,17,19,21,59). In addition to manual palpation or assessing pressure pain thresholds, such allodynia/hyperalgesia outside the segmental area of primary nociception can be established through history taking or questioning as well. For instance, a low back pain patient reporting that wearing a necklace is no longer possible as it triggers pain.

Here we propose criterion 1 as a go/no-go for the classification of CS pain. If criterion 1 and 2 are both met, then the classification of CS can be established. If only the first criterion (disproportionate pain) is met and not the second criterion, further screening of criterion 3 is required.

Criterion 3: Hypersensitivity of senses unrelated to the musculoskeletal system

CS may reflect much more than generalized hypersensitivity to pain: It may be characterized by an increased responsiveness to a variety of stimuli in addition to mechanical pressure (3,12,17,19,21,53,54,59), namely chemical substances (62), cold (21,42), heat (13,21), electrical stimuli (32,53), stress (31,63-66), emotions, and mental load. Given the overall hyper-responsiveness of central nervous system neurons, CS may explain the hypersensitivity to many environmental (bright light, cold/heat, sound/noise, weather, stress, food [67-69]), and chemical stimuli (62,70,71) (odors, pesticides, medication among others). It is therefore recommended to

question the patients with suspected CS for hypersensitivity to bright light, sound, smell, and hot or cold sensations. For classification purposes, these symptoms should not have been present prior to the onset of the pain (disorder) of interest here. However, some of these could have been present before pain. Their premorbid presence does not exclude the possibility of CS pain, but makes them unreliable for diagnosing CS pain.

Still, direct evidence showing that CS explains hypersensitivity to such environmental stimuli is lacking. This assumption is based on evidence from psychophysiological studies showing hypersensitivity in pain patients to mechanical pressure (3,12,17,19,21,53,54,59), cold (21,42), heat (13,21), electrical stimuli (32,53), stress (31,63-66), food (67-69), chemical stimuli (62,70,71), and a study in patients with fibromyalgia where low thresholds to auditory tones correlated with pressure pain thresholds (72). It is therefore recommended to question the patients with suspected CS for hypersensitivity to bright light, sound, smell, and hot or cold sensations.

The screening of criterion 3 can be done using part A of the Central Sensitization Inventory (44), which assesses symptoms common to CS, with total scores ranging from 0 to 100. Based on a validation study in a sample of 89 CS-pain patients and a 129 non-patient comparison group, a cutoff score of 40 is recommended (45). A cutoff score of 40 on the Central Sensitization Inventory provides a clinically relevant guide to alert health care professionals to the possibility that a patient's symptom presentation may indicate the presence of CS pain (45). Still, establishing CS pain in clinical situations should not rely on self-report only, and there is currently no published work comparing the Central Sensitization Inventory between CS and neuropathic pain patients. Hence, we have no direct evidence to support the use of the Central Sensitization Inventory as the sole criterion for classifying CS pain, and have therefore chosen to integrate its use in a more comprehensive approach to classifying CS pain.

Here we propose that the combination of a score of at least 40 on the Central Sensitization Inventory, together with disproportionate pain (criterion 1), suffices for the classification of CS pain in patients with non-neuropathic pain (Fig. 1).

Additional Signs and Symptoms Often Seen in Patients with CS, but Not Required for the Classification

Clearly, patients with CS typically present with many more signs and symptoms than those included in the 3

Table 2. *Additional signs and symptoms often seen in patients with central sensitization (CS), but not required for the classification of CS pain.*

Sign or symptom	Assessment	Description
Numbness	Questioning and/or clinical examination	Numbness not localized and with nonsegmental distribution
Muscle weakness	Questioning and/or clinical examination	Subjective sensation of weakness in whole limb/lack of muscle control in whole limb
Cognitive deficits	Questioning and/or clinical examination	Concentration difficulties, short-term memory disturbances, latency, difficulties finding the correct words, "brain fog"
Sleeping difficulties	Questioning	Difficulty falling asleep, frequent awakenings at night, unrefreshing sleep
Inconsistent clinical examination findings	Clinical examination	Inconsistent findings across clinical tests
Phantom swelling sensation	Questioning and/or clinical examination	Sensation of swollen limb in absence of visual evidence of edema or swelling
Phantom swelling enhancement	Questioning and/or clinical examination	Phantom swelling sensations enhance when the patients close their eyes
Phantom swelling diminishment	Questioning and/or clinical examination	Phantom swelling sensations decrease or disappear when they view the affected limb
Altered perception of affected body part	Questioning and/or clinical examination	Perception that the affected body part is smaller or larger than it should be, or inability to feel part of the affected body region without visual or tactile input
Impaired tactile localization	Questioning and/or clinical examination	Decreased tactile acuity of (the skin above) the affected region; increased 2-point discrimination threshold
Phantom stiffness	Questioning and/or clinical examination	Sensation of joint stiffness in absence of objective signs of decreased mobility
Dyskinaesthesia	Questioning and/or clinical examination	Sensation of clumsiness or poor spatial acuity or less aware of where their limbs are in space

classification criteria for CS. For instance, the longer pain persists, the more likely CS becomes a more dominant component to the clinical presentation (73). An abnormal timeline is defined as a course over time that deviates from the natural course of the illness or injury. Table 2 lists a number of additional signs and symptoms often seen in patients with CS pain. Some of them partly overlap with one or more of the classification criteria for CS pain. Others are totally new and did not make it into the classification criteria, either because our clinical and research experience indicates that their prevalence among patients with CS is too low, or because they are not specific for CS. Taken together, the additional signs and symptoms have low sensitivity or specificity for patients with CS, and are mainly included here for clarity reasons. If present, they may strengthen the classification of CS pain, but only if they have not been present prior to the onset of the pain (disorder) of interest.

In addition to the signs and symptoms listed in Table 2, it is often informative to question the patient about the short-term and long-term therapeutic responses to

previous or ongoing treatments. The following options can be regarded as an abnormal therapeutic response: nonresponders to nociception-targeted treatments provided, inconsistent or unpredictable response to treatment, intolerance to various treatment approaches, or an acute increase in hypersensitivity to various stimuli in response to (new) treatment, including symptom exacerbation beyond what is regularly seen in patients with local (nociceptive) pain disorders (25,73).

Finally, we acknowledge the close association between CS and maladaptive psychosocial factors (e.g., negative emotions, poor self-efficacy, maladaptive beliefs and pain behaviors), as evidenced in the study by Smart et al (39). Indeed, "cognitive emotional sensitization" (74) refers to the capacity of forebrain centers of exerting powerful influences on various nuclei of the brainstem, including the nuclei identified as the origin of the descending facilitatory pathways (75). The activity in descending pathways is not constant but can be modulated, for example by the level of vigilance, catastrophizing, depression, attention, and stress (76,77).

In spite of the evidence pointing to an important role for maladaptive psychosocial and emotional factors in the etiology and maintenance of the process of CS, we chose against including them in the criteria for classification of CS pain. The reason is based on research findings showing that depressive symptoms, anxiety, or catastrophizing are neither related to pain sensitivity or brain activity during experimental pain in chronic pain patients (78). In addition, the lack of sensitivity and specificity of maladaptive psychosocial and emotional factors for the classification of CS pain is an important issue. Maladaptive psychosocial and emotional factors can be present in chronic pain patients without CS as well, making them inappropriate for inclusion as a classification criterion. Likewise, patients with clear evidence of CS sometimes do not have negative emotions, maladaptive beliefs, or pain behaviors, indicating their low sensitivity for the classification of CS in patients with chronic pain. Nevertheless, the authors recognize the importance of assessing and addressing these psychosocial and emotional factors in the treatment approach of any pain patient.

Discussion

This is the first presentation of criteria and an algorithm for the clinical classification of CS in pain patients, supported by a large volume of research findings (1-4,8,12,14,15,32,39-42,45,53,59,62,73). Moreover, guidelines for the differential classification between neuropathic, nociceptive, and CS pain are proposed. In all 3 pain types a biopsychosocial view is warranted; in all 3 pain types a multimodal model is necessary to explain the pain (intensity) and to choose the appropriate treatment.

In addition, criterion 3 from the classification criteria proposed here is supported by a large validation study of the Central Sensitization Inventory, using patients with various CS diagnoses like restless leg syndrome, chronic fatigue syndrome, temporomandibular disorders, tension headaches, migraines, fibromyalgia, irritable bowel syndrome, and multiple chemical sensitivity syndromes (45). Finally, the classification criteria are directly substantiated by a study of a large group of patients with low back pain ($n = 464$) (40). Two of the 4 signs/symptoms that differentiated the CS low back pain patients from the neuropathic and nociceptive pain groups are included in the 4 major classification criteria for CS: pain disproportionate to the nature and extent of injury or pathology, and diffuse/nonanatomic areas of pain/tenderness on palpation (40). In addition

to these 2 signs/symptoms, a third sign (disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple/nonspecific aggravating/easing factors), although rather specific for spinal pain, is partly included in criteria 2 and 3.

In addition to the scientific evidence presented, these classification criteria are supported by expert consensus. Eighteen pain experts from 13 institutions across 7 countries combine over 100 years of clinical and scientific experience in patients with chronic pain, and over 200 scientific publications in the field of chronic pain. That said, the classification algorithm still requires validation in clinical settings, including examination of its clinical applicability. The inter- and intra-examiner test-retest reliability, sensitivity, specificity, positive, and negative likelihood ratios of the classification criteria presented here remain to be examined. In addition, the classification algorithm lacks "objective" criteria, but for the time being there is little proof for an objective biomarker for CS pain. However, this is the first step towards a set of classification criteria and a classification algorithm for CS pain. We hope our proposal will facilitate the acknowledgment and recognition of CS, research in this area, and eventually adaptation/improvement of the classification algorithm based on research data.

If a clinician recognizes CS in a patient with chronic pain, how does it potentially impact upon treatment? The presence of CS implies that the brain produces pain, fatigue, and other warning signs even when there is no real tissue damage. CS is not a disorder of the mind, but rather a disease of the brain and spinal cord. Hence, the brain should become an important treatment target. This can be achieved by explaining to the patient the mechanism of CS with evidence from modern neuroscience, an approach with high patient satisfaction (79-81), and has proven to be effective in a variety of chronic pain populations (80). Neuroscience education enables patients to understand the controversy surrounding their pain, including the lack of objective biomarkers, and the need for a time-contingent approach to activity and exercise therapy. A symptom-contingent approach may facilitate the brain in its production of nonspecific warning signs, while a time-contingent approach might deactivate brain-orchestrated descending facilitatory pathways. This view is supported by findings of reduced central nervous system hyperexcitability (37), and an increase in prefrontal cortical volume (38) in response to time-contingent therapy in chronic pain (fibromyalgia) patients.

In addition, centrally-acting drugs, like selective and balanced serotonin and norepinephrine reuptake inhibitor drugs, the serotonin precursor tryptophan, opioids, NMDA-receptor antagonists, and calcium channel $\alpha_2\delta$ ligands, are indicated for the treatment of CS (82). For more indepth guidelines on the treatment of CS in patients with chronic pain, the readers are referred to other sources (16,23,24,56,81,82).

CONCLUSION

The awareness is growing that CS is of prime importance for the management of chronic pain, but its classification is challenging clinically since no gold standard method of assessment exists. It is proposed that the classification of CS pain entails 2 major steps: the exclusion of neuropathic pain and the differential classification of nociceptive versus CS pain. For the former, the International Association for the Study of Pain diagnostic criteria (46) are available for diagnosing or excluding neuropathic pain, although they require

validation work as well. For the latter, clinicians are advised to screen their patients for 3 major classification criteria, and use them to complete the classification algorithm for each individual patient with chronic pain. Although based on both research findings and expert opinion, the classification algorithm requires experimental testing in future studies.

Disclaimer

There was no external funding in the preparation of this manuscript.

Conflict of interest

Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

REFERENCES

- Herren-Gerber R, Weiss S, Arendt-Nielsen L, Petersen-Felix S, Di Stefano G, Radanov BP, Curatolo M. Modulation of central hypersensitivity by nociceptive input in chronic pain after whiplash injury. *Pain Med* 2004; 5:366-376.
- Jull G, Sterling M, Kenardy J, Beller E. Does the presence of sensory hypersensitivity influence outcomes of physical rehabilitation for chronic whiplash? A preliminary RCT. *Pain* 2007; 129:28-34.
- Sterling M, Treleaven J, Edwards S, Jull G. Pressure pain thresholds in chronic whiplash associated disorder: Further evidence of altered central pain processing. *J Musculoskel Pain* 2002; 10:69-81.
- Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. *Pain* 2003; 104:509-517.
- Yang CC, Lee JC, Kromm BG, Ciol MA, Berger R. Pain sensitization in male chronic pelvic pain syndrome: Why are symptoms so difficult to treat? *J Urol* 2003; 170:823-826.
- Farmer MA, Chanda ML, Parks EL, Baliki MN, Apkarian AV, Schaeffer AJ. Brain functional and anatomical changes in chronic prostatitis/chronic pelvic pain syndrome. *J Urol* 2011; 186:117-124.
- Giesecke T, Gracely RH, Grant MA, Nachemson A, Petzke F, Williams DA, Clauw DJ. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheumatism* 2004; 50:613-623.
- Staud R. Evidence for shared pain mechanisms in osteoarthritis, low back pain, and fibromyalgia. *Curr Rheumatol Rep* 2011; 13:513-520.
- Roussel N, Nijs J, Meeus M, Mylius V, Fayt C, Oostendorp RAB. Central sensitization and altered central pain processing in chronic low back pain: Fact or myth? *Clin J Pain* 2013; 29:625-663.
- Vierck CJ. Mechanisms underlying development of spatial distributed chronic pain (fibromyalgia). *Pain* 2006; 124:242-263.
- Meeus M, Nijs J. Central sensitization: A biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol* 2007; 26:465-473.
- Paul TM, Soo Hoo J, Chae J, Wilson RD. Central hypersensitivity in patients with subacromial impingement syndrome. *Arch Phys Med Rehabil* 2012; 93:2206-2209.
- Meeus M, Nijs J, Van de Wauwer N, Toeback L, Truijten S. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: An experimental study. *Pain* 2008; 139:439-448.
- Buchgreitz L, Egsgaard LL, Jensen R, Arendt-Nielsen L, Bendtsen L. Abnormal pain processing in chronic tension-type headache: A high-density EEG brain mapping study. *Brain* 2008; 131:3232-3238.
- de Tommaso M, Federici A, Franco G, Ricci K, Lorenzo M, Delussi M, Vecchio E, Serpino C, Livrea P, Todarello O. Suggestion and pain in migraine: A study by laser evoked potentials. *CNS Neurol Disord Drug Targets* 2012; 11:110-126.
- Mease PJ, Hanna S, Frakes EP, Altman RD. Pain mechanisms in osteoarthritis: Understanding the role of central pain and current approaches to its treatment. *J Rheumatol* 2011; 38:1546-1551.
- Suokas AK, Walsh DA, McWilliams DF, Condon L, Moreton B, Wyld V, Arendt-Nielsen L, Zhang W. Quantitative sensory testing in painful osteoarthritis: A systematic review and meta-analysis. *Osteoarthritis and Cartilage* 2012; 20:1075-1085.
- Meeus M, Vervisch S, De Clerck LS,

- Moorkens G, Hans G, Nijs J. Central sensitization in patients with rheumatoid arthritis: A systematic literature review. *Semin Arthritis Rheum* 2012; 41:556-567.
19. Fernández-Carnero J, Fernández-de-Las-Peñas C, de la Llave-Rincón AI, Ge HY, Arendt-Nielsen L. Widespread mechanical pain hypersensitivity as sign of central sensitization in unilateral epicondylalgia: A blinded, controlled study. *Clin J Pain* 2009; 25:555-561.
 20. Coombes BK, Bisset L, Vicenzino B. Thermal hyperalgesia distinguishes those with severe pain and disability in unilateral lateral epicondylalgia. *Clin J Pain* 2012; 28:595-601.
 21. Moloney N, Hall T, Doody C. Sensory hyperalgesia is characteristic of non-specific arm pain. A comparison with cervical radiculopathy and pain-free controls. *Clin J Pain* 2013; 29:948-956.
 22. van Wilgen CP, Konopka KH, Keizer D, Zwerver J, Dekker R. Do patients with chronic patella tendinopathy have an altered somatosensory profile? – A Quantitative Sensory Testing (QST) study. *Scand J Sport Med* 2013; 23:149-155.
 23. Nijs J, Van Houdenhove B. From acute musculoskeletal pain to chronic widespread pain and fibromyalgia: Application of pain neurophysiology in manual therapy practice (Masterclass). *Manual Ther* 2009; 14:3-12.
 24. Nijs J, Van Oosterwijck J, De Hertogh W. Rehabilitation of chronic whiplash: Treatment of cervical dysfunctions or chronic pain syndrome? *Clin Rheumatol* 2009; 28:243-251.
 25. Nijs J, Van Houdenhove B, Oostendorp RAB. Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice (Masterclass). *Manual Ther* 2010; 15:135-141.
 26. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. *Pain* 2011; 152:S2-S15.
 27. Staud R, Craggs JG, Robinson ME, Perlstein WM, Price DD. Brain activity related to temporal summation of C-fiber evoked pain. *Pain* 2007; 129:130-142.
 28. Seifert F, Maihöfner C. Central mechanisms of experimental and chronic neuropathic pain: Findings from functional imaging studies. *Cell Mol Life Sci* 2009; 66:375-390.
 29. Lee MC, Zambreau L, Menon DK, Tracey I. Identifying brain activity specifically related to the maintenance and perceptual consequence of central sensitization in humans. *J Neurosci* 2008; 28:11642-11649.
 30. Zhuo M. A synaptic model for pain: long-term potentiation in the anterior cingulate cortex. *Mol Cells* 2007; 23:259-271.
 31. Suarez-Roca H, Leal L, Silva JA, Pinerua-Shuhaibar L, Quintero L. Reduced GABA neurotransmission underlies hyperalgesia induced by repeated forced swimming stress. *Behav Brain Res* 2008; 189:159-169.
 32. Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, Curatolo M. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. *Pain* 2004; 107:7-15.
 33. Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci* 2012; 15:1117-1119.
 34. Van Oosterwijck J, Nijs J, Meeus M, Truijzen S, Craps J, Van den Keybus N, Paul L. Pain neurophysiology education improves cognitions, pain thresholds and movement performance in people with chronic whiplash: A pilot study. *J Rehabil Res Devel* 2011; 48:43-58.
 35. Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Oullet JA, Stone LS. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *J Neurosci* 2011; 31:7540-7550.
 36. Moseley GL. Widespread brain activity during and abdominal task markedly reduced after pain physiology education: fMRI evaluation of a single patient with chronic low back pain. *Austr J Physiother* 2005; 51:49-52.
 37. Ang DC, Chakr R, Mazzuca S, France CR, Steiner J, Stump T. Cognitive-behavioral therapy attenuates nociceptive responding in patients with fibromyalgia: A pilot study. *Arthritis Care Res* 2010; 62:618-623.
 38. de Lange FP, Koers A, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome. *Brain* 2008; 131:2172-2180.
 39. Smart KM, Blake C, Staines A, Doody C. Self-reported pain severity, quality of life, disability, anxiety and depression in patients classified with “nociceptive,” “peripheral neuropathic” and “central sensitization” pain. The discriminant validity of mechanisms-based classifications of low back (±leg) pain. *Manual Ther* 2012; 17:119-125.
 40. Smart KM, Blake C, Staines A, Thacker M, Doody C. Mechanisms-based classifications of musculoskeletal pain: part 1 of 3: Symptoms and signs of central sensitization in patients with low back (±leg) pain. *Manual Ther* 2012; 17:336-344.
 41. Smart KM, Blake C, Staines A, Doody C. The discriminative validity of “nociceptive,” “peripheral neuropathic,” and “central sensitization” as mechanisms-based classifications of musculoskeletal pain. *Clin J Pain* 2011; 27:655-663.
 42. Kasch H, Querama E, Flemming WB, Jensen TS. Reduced cold pressor pain tolerance in non-recover whiplash patients: A 1-year prospective study. *Eur J Pain* 2005; 9:561-569.
 43. Ruscheweyh R, Marziniak M, Stumpenhorst F, Reinholz J, Knecht S. Pain sensitivity can be assessed by self-rating: Development and validation of the Pain Sensitivity Questionnaire. *Pain* 2009; 146:65-74.
 44. Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, Perez Y, Gatchel RJ. The development and psychometric validation of the central sensitization inventory. *Pain Pract* 2012; 12:276-285.
 45. Neblett R, Cohen H, Choi YH, Hartzell MM, Williams M, Mayer TG, Gatchel RJ. The Central Sensitization Inventory (CSI): Establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *J Pain* 2013; 14:438-445.
 46. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. *Neurology* 2008; 70:1630-1635.
 47. Cohen SP, Mao A. Neuropathic pain: Mechanisms and their clinical implications. *Brit Med J* 2014; 348:f7656. doi: 10.1136/bmj.f7656.
 48. Baron R, Binder A, Wasner G. Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010; 9:807-819.
 49. Haanpää M, Treede RD. Diagnosis and classification of neuropathic pain. *Pain Clinical Updates* 2010; XVII.

50. Haanpää M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, Cruccu G, Hansson P, Haythornthwaite JA, Iannetti GD, Jensen TS, Kaupilla T, Nurmikko TJ, Rice AS, Rowbotham M, Serra J, Sommer C, Smith BH, Treede RD. NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011; 152:14-27.
51. Sterling M, Jull G, Vicenzino B, Kenardy J. Characterization of acute whiplash-associated disorders. *Spine* 2004; 29:182-188.
52. Purves D, Augustine GJ, Fitzpatrick D, Katz LC, LaMantia A-S, McNamara. Pain. In: Purves D, Augustine GJ, Fitzpatrick D, Katz LC, LaMantia A-S, McNamara (eds). *Neuroscience*. Sinauer Associates, Inc., Sunderland, 1997 p 167.
53. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, Dayer P, Vischer TL. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheumatism* 2003; 48:1420-1429.
54. Yunus MB. Fibromyalgia and overlapping disorders: The unifying concept of central sensitivity syndromes. *Sem Arthritis Rheumatol* 2007; 36:330-356.
55. Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, Graven-Nielsen T. Sensitization in patients with painful knee osteoarthritis. *Pain* 2010; 149:573-581.
56. Murphy SL, Phillips K, Williams DA, Clauw DJ. The role of the central nervous system in osteoarthritis pain and implications for rehabilitation. *Curr Rheumatol Rep* 2012; 14:576-582.
57. Lluch Girbes E, Nijs J, Torres Cueco R, López Cubas C. Pain treatment for patients with osteoarthritis and central sensitization. *Phys Ther* 2013; 93:842-851.
58. Parks EL, Geha PY, Baliki MN, Katz J, Schnitzer TJ, Apkarian AV. Brain activity for chronic knee osteoarthritis: Dissociating evoked pain from spontaneous pain. *Eur J Pain* 2011; 15:843.
59. Meeus M, Nijs J, Huybrechts S, Truijen S. Evidence for generalized hyperalgesia in chronic fatigue syndrome: A case control study. *Clin Rheumatol* 2010; 29:393-398.
60. Margolis RB, Tait RC, Krause SJ. A rating system for use with patient pain drawings. *Pain* 1986; 24:57-65.
61. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis Rheum* 1990; 33:160-172.
62. Morris VH, Cruwys SC, Kidd BL. Characterisation of capsaicin-induced mechanical hyperalgesia as a marker for altered nociceptive processing in patients with rheumatoid arthritis. *Pain* 1997; 71:179-186.
63. Khaser SG, Burkhart J, Dina OA, Brown AS, Bogen O, Alessandri-Haber N, Green PG, Reichling DB, Levine JD. Stress induces a switch of intracellular signaling in sensory neurons in a model of generalized pain. *J Neurosci* 2008; 28:5721-5730.
64. Quintero L, Montero M, Avila C, Arcaya JL, Suarez-Roca H. Long-lasting delayed hyperalgesia after subchronic swim stress. *Pharmacol Biochem Behav* 2000; 67:449-458.
65. Martenson ME, Cetas JS, Heinricher MM. A possible neural basis for stress-induced hyperalgesia. *Pain* 2009; 142:236-244.
66. McLean SA, Clauw DJ, Abelson JL, Liberzon I. The development of persistent pain and psychological morbidity after motor vehicle collision: Integrating the potential role of stress response systems into a biopsychosocial model. *Psychosom Med* 2005; 67:783-790.
67. van Nieuwenhoven MA, Kilkens TO. The effect of acute serotonergic modulation on rectal motor function in diarrhea-predominant irritable bowel syndrome and healthy controls. *Eur J Gastroenterol Hepatol* 2012; 24:1259-1265.
68. Zhou Q, Verne GN. New insights into visceral – hypersensitivity – clinical implications in IBS. *Nat Rev Gastroenterol Hepatol* 2011; 8:349-355.
69. Barbara G, Cremon C, De Giorgio R, Dohel G, Zecchi L, Bellacosa L, Carini G, Stanghellini V, Corinaldesi R. Mechanisms underlying visceral hypersensitivity in irritable bowel syndrome. *Curr Gastroenterol Rep* 2011; 13:308-315.
70. Graversen C, Brock C, Drewes AM, Farina D. Biomarkers for visceral hypersensitivity identified by classification of electroencephalographic frequency alterations. *J Neural Eng* 2011; 8:056014. doi: 10.1088/1741-2560/8/5/056014.
71. Holst H, Arendt-Nielsen L, Mosbech H, Elberling J. Increased capsaicin-induced secondary hyperalgesia in patients with multiple chemical sensitivity. *Clin J Pain* 2011; 27:156-162.
72. Gerster JC, Hadji-Djilani A. Hearing and vestibular abnormalities in primary fibrositis syndrome. *J Rheumatol* 1984; 11:678-680.
73. Smart KM, Blake C, Staines A, Doody C. Clinical indicators of “nociceptive,” “peripheral neuropathic” and “central” mechanisms of musculoskeletal pain. A Delphi survey of expert clinicians. *Manual Ther* 2010; 15:80-87.
74. Brosschot JF. Cognitive-emotional sensitization and somatic health complaints. *Scand J Psychol* 2002; 43:113-121.
75. Zusman M. Forebrain-mediated sensitization of central pain pathways: “Non-specific” pain and a new image for MT. *Manual Ther* 2002; 7:80-88.
76. Rygh LJ, Tjolsen A, Hole K, Svendsen F. Cellular memory in spinal nociceptive circuitry. *Scand J Psychol* 2002; 43:153-159.
77. Rivest K, Côté JN, Dumas J-P, Sterling M, De Serres SJ. Relationships between pain thresholds, catastrophizing and gender in acute whiplash injury. *Manual Ther* 2010; 15:154-159.
78. Jensen KB, Petzke F, Carville S, Fransson P, Marcus H, Williams SC, Choy E, Mainguy Y, Gracely R, Ingvar M, Kosek E. Anxiety and depressive symptoms in fibromyalgia are related to poor perception of health but not to pain sensitivity or cerebral processing of pain. *Arthritis Rheum* 2010; 62:3488-3495.
79. Meeus M, Nijs J, Van Oosterwijck J, Van Alsenoy V, Truijen S, De Meirleir K. Pain physiology education improves pain beliefs in patients with chronic fatigue syndrome compared to pacing and self-management education: A double-blind randomized controlled trial. *Arch Phys Med Rehabil* 2010; 91:1153-1159.
80. Louw A, Diener I, Butler DS, Puentedura EJ. The effect of neuroscience education on pain, disability, anxiety, and stress in chronic musculoskeletal pain. *Arch Phys Med Rehabil* 2011; 92:2041-2056.
81. Nijs J, Paul van Wilgen C, Van Oosterwijck J, van Ittersum M, Meeus M. How to explain central sensitization to patients with “unexplained” chronic musculoskeletal pain: practice guidelines. *Manual Ther* 2011; 16:413-418.
82. Nijs J, Meeus M, Van Oosterwijck J, Roussel N, De Kooning M, Ickmans K, Matic M. Treatment of central sensitization in patients with “unexplained” chronic pain: What options do we have? *Expert Opin Pharmacother* 2011; 12:1087-1098.

