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Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice

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ABSTRACT

Central sensitization plays an important role in the pathophysiology of numerous musculoskeletal pain disorders, yet it remains unclear how manual therapists can recognize this condition. Therefore, mechanism based clinical guidelines for the recognition of central sensitization in patients with musculoskeletal pain are provided. By using our current understanding of central sensitization during the clinical assessment of patients with musculoskeletal pain, manual therapists can apply the science of nociceptive and pain processing neurophysiology to the practice of manual therapy. The diagnosis/assessment of central sensitization in individual patients with musculoskeletal pain is not straightforward, however manual therapists can use information obtained from the medical diagnosis, combined with the medical history of the patient, as well as the clinical examination and the analysis of the treatment response in order to recognize central sensitization. The clinical examination used to recognize central sensitization entails the distinction between primary and secondary hyperalgesia.

1. Introduction

Even with acute pain the nervous system undergoes some changes. When tissue is damaged and pain persists for a few days with adaptation of unimodal nociceptors, the responsiveness of polymodal nociceptive endings is enhanced by substances released from various sources (i.e. serotonin released by platelets) (Purves et al., 1997). This process is called primary hyperalgesia or peripheral sensitization of nociceptors, and represents a protective action by the human body in order to prevent further use of damaged structures and consequent further damage of the traumatized and surrounding tissues. Secondary hyperalgesia refers to increased responsiveness of dorsal horn neurons localized in the spinal segments of the primary source of nociception. While peripheral sensitization is a local phenomenon, central sensitization is a central process of the nervous system.

Central sensitization is defined as an augmentation of responsiveness of central neurons to input from unimodal and polymodal receptors (Meyer et al., 1995). Central sensitization encompasses altered sensory processing in the brain (Staud et al., 2007), malfunctioning of descending anti-nociceptive mechanisms (Meeus et al., 2008), increased activity of pain facilitatory pathways, temporal summation of second pain or wind-up (Meeus and Nijs, 2007; Staud et al., 2007), and long-term potentiation of neuronal synapses in the anterior cingulate cortex (Zhuo, 2007). Besides top-down mechanisms included in the pathophysiology of central sensitization, it is important to realize that there are bottom-up mechanisms as well (Fig. 1). For example, peripheral injury and other forms of stressors trigger the release of pro-inflammatory cytokines, with the consequent activation of spinal cord glia with cyclooxygenase-2 and prostaglandin E2 expression in the central nervous system (Maier and Watkins, 1998; Watkins and Maier, 1999; Bazan, 2001; Samad et al., 2001). The outcome of the processes involved in central sensitization is an increased responsiveness to a variety of peripheral stimuli including mechanical pressure, chemical substances, light, sound, cold, heat, and electrical stimuli. The increased sensitivity to variable stimuli results in a large decreased load tolerance of the senses and the

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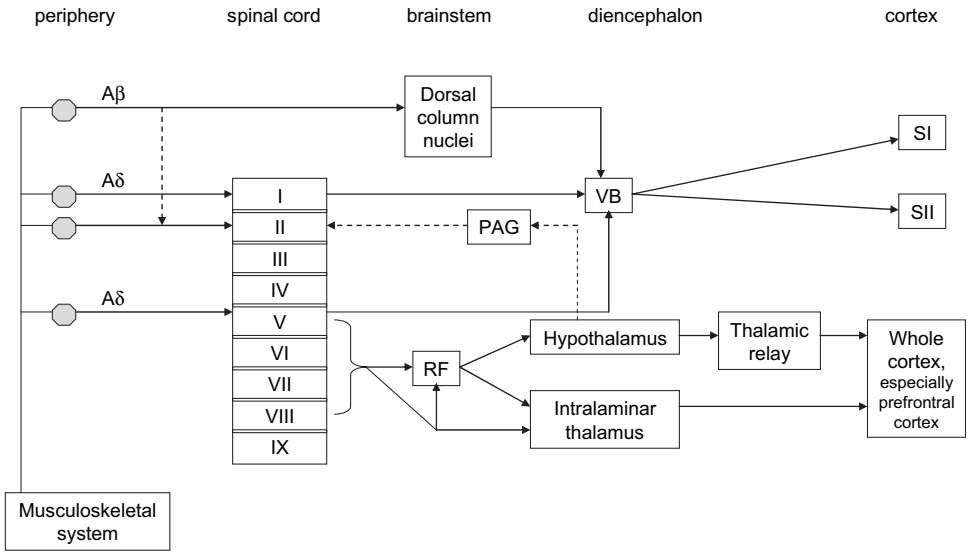

Fig. 1. Simplified block diagram displaying nociceptive processing in the nervous system. Input from the musculoskeletal system is transferred through Aδ and C nociceptive fibres and low threshold Aβ fibres. Dashed lines represent inhibiting (mainly descending) pathways, the ultimate effect of which is inhibitory in lamina II of the spinal cord. Numbers I–IX represent the corresponding laminae of the spinal cord. RF, reticular formation; PAG, periaqueductal grey matter; VB, ventrobasal nuclear complex of the thalamus; SI, primary somatosensory cortex; SII, secondary somatosensory cortex. Modified from: Wells et al. (1996, Fig. 8.3).

neuromusculoskeletal system. Further details addressing the pathophysiology of central sensitization is beyond the scope of the present manuscript; interested readers are referred to Fig. 1 and comprehensive reviews on the subject (Vierck, 2006; Nielsen and Henriksson, 2007; Yunus, 2007a).

Central sensitization is frequently present in various chronic musculoskeletal pain disorders, including chronic whiplash associated disorders (Curatolo et al., 2001), temporomandibular disorders (Maixner et al., 1998), chronic low back pain (Giesecke et al., 2004), rheumatoid arthritis (Yunus, 2007b), fibromyalgia (Vierck, 2006), as well as others. The presence of central sensitization in patients with musculoskeletal pain implies an increased complexity of the clinical picture (i.e. an increase in unrelated symptoms and hence a more difficult clinical reasoning process) (Nijs et al., 2009), as well as decreased odds for a favorable rehabilitation outcome (Jull et al., 2007). Guidelines for the prevention and treatment of central sensitization in patients with musculoskeletal pain have been presented elsewhere (Nijs and Van Houdenhove, 2009; Nijs et al., 2009). These guidelines enable clinicians to consider conservative treatments, including manual therapy skills, for the process of central sensitization in patients with chronic whiplash associated disorders (Nijs et al., 2009) and fibromyalgia (Nijs and Van Houdenhove, 2009). However, it remains unclear how manual therapists can recognize the process of central sensitization in individual patients. For some therapists, central sensitization remains a theoretical concept that is unlikely to occur in the patients they are treating. Therefore, increasing awareness for the possibility of central sensitization occurring in patients with musculoskeletal pain is useful in daily clinical practice.

The present manuscript provides clinical guidelines for the recognition and assessment of central sensitization in patients with musculoskeletal pain. Currently, an international consensus definition or clinical criteria for central sensitization is essentially lacking. A body of scientific literature reporting original data of signs and symptoms in relation to established measures of central sensitization in patients with musculoskeletal pain is currently available (e.g. Curatolo et al., 2001; Desmeules et al., 2003; Banic et al., 2004; Meeus et al., 2008), and is used here to provide clinical guidelines for the recognition and assessment of central sensitization. Application of our current understanding of central sensitization in the clinical assessment of patients with musculoskeletal pain will allow manual therapists to apply the science of pain neurophysiology to the practice of manual therapy.

2. Using the medical diagnosis to recognize central sensitization

Central sensitivity syndromes is a term first used by Yunus in 2000 to describe a group of overlapping conditions bound by a common pathophysiological mechanism of central sensitization (Yunus, 2007a). Many patients present in clinical practice with a medical diagnosis that was established by a physician. In a number of cases, the medical diagnosis can provide the clinician with important information in relation to central sensitization. Of relevance, a body of literature is available linking medical diagnosis to central sensitization. Here, the scientific literature can be applied to manual therapy practices. In some cases, such as fibromyalgia (Nielsen and Henriksson, 2007; Meeus and Nijs, 2007; Yunus, 2007a) and chronic fatigue syndrome (Meeus and Nijs, 2007; Meeus et al., 2008), the medical diagnosis most often implies the presence of central sensitization. If the clinical picture as well as the symptom presentation (see below) matches the presence of central sensitization in patients with these types of diagnoses, then manual therapists can conclude that central sensitization is present. Hence, therapists should account for the processes involved in central sensitization when applying therapy.

However, in many cases it is not an all-or-nothing situation. Many medical diagnoses (e.g. non-specific low back pain, whiplash associated disorders) are associated but not uniformly characterized by central sensitization (Table 1). In these cases, the clinician should be aware of the possibility that central sensitization is present. However, the possibility exists that central sensitization does not play a role in the patient's complex clinical picture.

In order to illustrate the reasoning presented above, let us take a closer look at some medical diagnoses frequently seen in manual therapy practice. While there is consistent evidence for altered central processing of nociception and central sensitization in people with chronic whiplash associated disorders (Curatolo et al.,

Table 1
Medical diagnosis associated with an increased likelihood for central sensitization.[a]

Medical diagnosis	Central sensitization is a characteristic of the disorder	Central sensitization is present in a subgroup
Chronic low back pain		✓
Chronic whiplash associated disorders	✓	
(Sub)acute whiplash associated disorders		✓
Temporomandibular disorders		✓
Myofascial pain syndrome		✓
Osteoarthritis		✓
Rheumatoid arthritis		✓
Fibromyalgia	✓	
Chronic fatigue syndrome	✓	
Chronic headache		✓
Irritable bowel syndrome	✓	

[a] Based on evidence from scientific studies (Langemark et al., 1993; Morris et al., 1997; Maixner et al., 1998; Burnstein et al., 2000; Curatolo et al., 2001; Weissman-Fogel et al., 2003; Giesecke et al., 2004; Wolfe and Michaud, 2004; Pielsticker et al., 2005; Schmidt-Wilcke et al., 2006; Vierck, 2006; Yunus, 2007b; Meeus et al., 2008).

2001; Sterling et al., 2003, 2006; Herren-Gerber et al., 2004), central sensitization is not present in *all* whiplash cases and is not a feature of chronic idiopathic neck pain (Scott et al., 2005). Typically, only a minority of acute whiplash patients develop chronic symptoms. Abnormal nociceptive processing appears very soon (<7 days) after the initial whiplash trauma, and once present it has important predictive ability for the development of chronic whiplash associated disorders (Sterling et al., 2003, 2006; Kasch et al., 2005). Thus, not all (sub)acute patients are characterized by central sensitization, however manual therapists should be aware of this possibility.

Another example is chronic non-specific low back pain. Some studies provided evidence in support of the presence of central sensitization in patients with non-specific chronic low back pain (Giesecke et al., 2004; Schmidt-Wilcke et al., 2006), while others refute such an association (Hoffman et al., 2005; Julien et al., 2005). It is concluded that central sensitization is present in some cases of chronic non-specific low back pain, possibly representing one of the subgroups of this frequent musculoskeletal disorder (Wand and O'Connell, 2008).

The myofascial variety within the heterogeneous group of temporomandibular disorders is also characterized by central sensitization (Yunus, 2007a). Likewise, regional chronic pain conditions that present with tender and/or trigger points in the absence of structural pathology (frequently referred to as myofascial pain syndrome) should alert the manual therapist to the possibility that central sensitization is determining the clinical picture (Yunus, 2007a). However, to our knowledge available evidence in support of central sensitization in patients with myofascial pain syndrome is limited to chronic whiplash associated disorders, temporomandibular disorders and chronic non-specific low back pain.

Furthermore, various subgroups of headache, chronic tension-type headache (Langemark et al., 1993; Pielsticker et al., 2005) and migraine (Burnstein et al., 2000; Weissman-Fogel et al., 2003) can be viewed as central sensitivity syndromes. Finally, rheumatoid arthritis and osteoarthritis are examples of local musculoskeletal disorders possibly causing continuous activation of polymodal nociceptors that initiate or sustain central sensitization (Yunus, 2007a). Although an important subgroup (20–35%) of patients with rheumatoid arthritis fulfil the diagnostic criteria for fibromyalgia (Wolfe and Michaud, 2004), research evidence in support of central sensitization is currently lacking. One study found evidence in support of enhanced central mechanisms in rheumatoid arthritis that in turn contributed to clinical features, including tenderness of peripheral joints (Morris et al., 1997). However, their data points to secondary hyperalgesia rather than central sensitization.

3. History taking in order to recognize central sensitization

Simply listening to the story of the patient (Van Houdenhove, 2004) will provide a number of clues that potentially point towards the presence of sensitization of the central nervous system. Central sensitization entails much more than generalized hypersensitivity to pain: it is characterized by an increased responsiveness to a variety of stimuli including mechanical pressure (Desmeules et al., 2004), chemical substances (Morris et al., 1997), cold temperature (Kasch et al., 2005), heat temperature (Meeus et al., 2008), electrical stimuli (Banic et al., 2004; Desmeules et al., 2004), stress, emotions, and mental load. The clinical picture is suggestive of a general intolerance to all kinds of physical and emotional stressors and hence a large decreased load tolerance of the human body in general. It is therefore recommended to question the patients with suspected central sensitization regarding their hypersensitivity to bright light, sound, smell, hot or cold sensations, pressure, touch and mechanical loading (Table 2). Some patients spontaneously mention that a hug by their partner can be painful. Others wear sunglasses inside buildings even during the winter time, while others turn down the radio volume even when it is already low. These examples make it easy to recognize hypersensitivity to pressure, light and sound respectively. Hyper-responsiveness to mechanical stimuli entails exaggerated responses to touch and active and passive movement. The latter two can be further assessed during the physical examination.

In addition, less obvious symptoms may also be related to central sensitization. Although there is currently no convincing evidence in support of their association with central sensitization, 'central' symptoms such as fatigue, concentration difficulties, sleep disturbances, and non-refreshing sleep are all frequently experienced by patients with central sensitization (Wolfe et al., 1990, Yunus, 2007b). Thus, questioning the patient with musculoskeletal pain about the presence of these symptoms might be warranted when searching for central sensitization.

When using Table 2 for the recognition of central sensitization in clinical practice, one must be careful when interpreting symptoms such as increased sensitivity to mechanical pressure, heat, or cold.

Table 2
Symptoms related to the presence of central sensitization.

Symptom	Characteristic of CS	Might be related to CS
Hypersensitivity to bright light	✓	
Hypersensitivity to touch	✓	
Hypersensitivity to noise	✓	
Hypersensitivity to pesticides	✓	
Hypersensitivity to mechanical pressure	✓	
Hypersensitivity to medication	✓	
Hypersensitivity to temperature (high and low)	✓	
Fatigue		✓
Sleep disturbances		✓
Unrefreshing sleep		✓
Concentration difficulties		✓
Swollen feeling (e.g. in limbs)		✓
Tingling		✓
Numbness		✓

CS, central sensitization.

'Hypersensitivity' generally means widespread rather than local or peripheral hypersensitivity to certain stimuli. In addition, it is important to realize that none of the symptoms listed above have strong diagnostic value for central sensitization. Rather, they each represent clues potentially pointing towards central sensitization. When two or three of these symptoms are present, searching for additional proof for central sensitization during the clinical examination is warranted. Even in the absence of a medical diagnosis known to be related to central sensitization, the presence of symptoms characteristic of central sensitization should alert the manual therapist. A flow diagram representing the diagnostic clinical reasoning process in case of suspected central sensitization is presented in Fig. 2.

In addition to the symptoms related to central sensitization explained above, other types of information reported by the patient can be of value in recognizing central sensitization. Firstly, the presence of a local pain condition prior to the onset of a trauma or injury increases the probability for developing peripheral and central sensitization. This is evidenced by research data in people with whiplash associated disorders (Carstensen et al., 2008). The premorbid pain condition can be localized at the same location or at a site distinct from the current condition. Secondly, at least in the bottom-to-top model (Nielsen and Henriksson, 2007), an ongoing source of peripheral nociception is required before the process of peripheral sensitization can establish central sensitization (Nijs and Van Houdenhove, 2009). Tissue injury healing and focal pain recovery should occur as soon as possible to prevent development of central sensitization (Vierck, 2006). Examples that fit within this model are those patients with long-standing musculoskeletal pain due to rheumatoid arthritis, a severe whiplash injury and patients reporting several unsuccessful treatment attempts. All these cases can be categorized under the heading 'abnormal disease course', despite the fact that the primary source of nociception remains the same (or decreases or even disappears), the symptom area and symptom severity increases. Thus, questioning the patient about the disease course, recovery course and premorbid medical conditions might provide the clinician with important information in relation to central sensitization.

4. Clinical examination to recognize central sensitization

When central sensitization is suspected based on the medical diagnosis and the information gathered during the history taking of the patient, the manual therapist may wish to examine the patient's response to certain stimuli (Fig. 2). The goals for using clinical tests assessing sensory processing can be diverse. Firstly, they may be used to establish the presence of central sensitization (diagnostic purpose). Secondly, they can be used to assess the severity of central sensitization. Thirdly, they can monitor pre- versus post-treatment progression of central sensitization. Finally, they can be used to determine the appropriate treatment parameters (e.g. intensity, amplitude and frequency of various manual therapy techniques).

One of the main characteristics of central sensitization in patients with musculoskeletal pain is a generalized rather than a localized decrease in their pressure pain threshold. Here, 'generalized' implies more than a segmental spreading of the symptom area, in that it means that the increased sensitivity is localized at sites segmentally unrelated to the primary source of nociception (e.g. the lower limbs in case of a whiplash trauma). Lower pressure pain thresholds at symptomatic areas most often represent primary hyperalgesia due to sensitized polymodal nociceptors within injured musculoskeletal structures. By measuring pressure pain thresholds outside the area of primary nociception, widespread hyperalgesia or secondary hyperalgesia can be detected. In cases of secondary hyperalgesia, a reduced pressure pain threshold in the various tissues innervated by the same segment (or two neighboring segments) can be detected. Findings of numerous areas of hyperalgesia at sites outside and remote from the symptomatic site, together with a non-segmental general decrease in

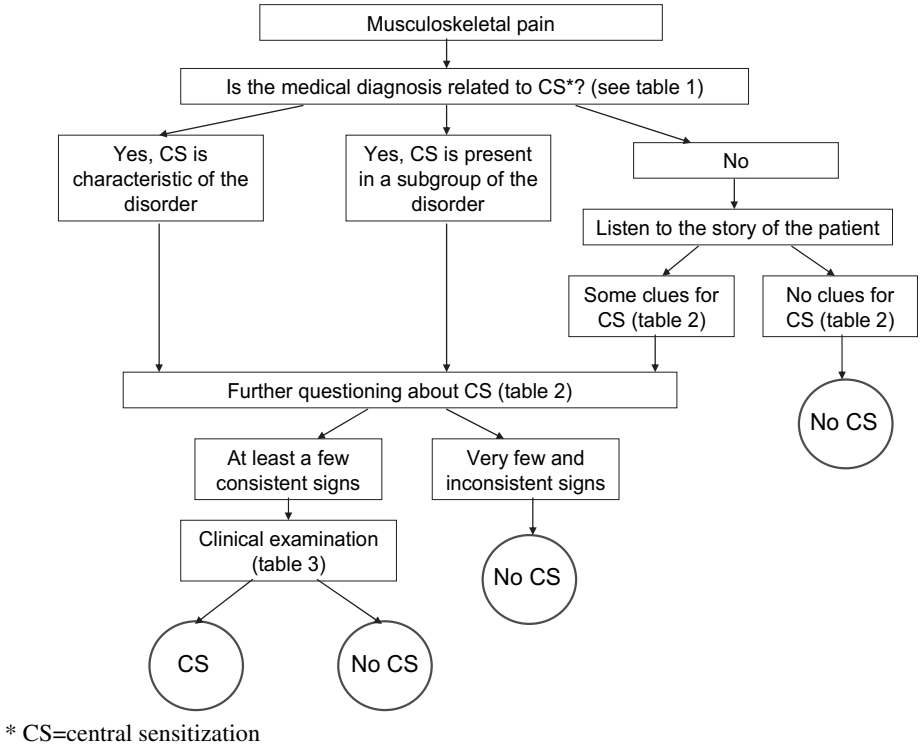

Fig. 2. Diagnostic clinical reasoning process to recognize central sensitization. CS, central sensitization.

pressure pain threshold, may imply a generalized hyperexcitability of central nociceptive pathways (Sterling et al., 2004).

Based on this reasoning, research has shown evidence in support of generalized hypersensitivity to mechanical pressure in patients with chronic whiplash associated disorders (Koelbaek Johansen et al., 1999; Sterling et al., 2004), as well as in a subgroup of the chronic low back pain population (Giesbrecht and Battie, 2005). To apply this to clinical practice, pressure pain threshold can be assessed using commercially available pressure algometers. A pressure pain threshold below 4 kg/cm^2 can be used to identify points of increased sensitivity to pressure (Wolfe et al., 1990). Pressure algometry provides a reliable and valid measure of the pressure pain threshold (Vanderweeen et al., 1996; Farasyn and Meeusen, 2003). In the absence of a pressure algometer, manual palpation can be used. Even when a manual therapist is not suspecting central sensitization, the finding of generalized hypersensitivity to manual palpation during routine clinical examination should alert the clinician.

Hypersensitivity to other stimuli can be demonstrated clinically by using a cold or hot item and placing it for a couple of seconds on the skin (e.g. a cold pack). Depending on the temperature, the cold or hot item should be perceived as cold or hot respectively, but should not elicit pain. If it does trigger pain, then localized hypersensitivity to cold or heat is established. Again, findings of numerous areas of cold or heat hyperalgesia located at sites outside and remote from the symptomatic site are crucial for differentiating primary or secondary hyperalgesia from generalized hyperalgesia. Likewise, augmented responses to sensory testing or mechanical stimuli like vibration at sites remote from the primary source of nociception (e.g. the medial malleolus in a patient with chronic shoulder pain) can generate important information addressing central sensitization. Quantitative sensory testing is suitable for assessing the presence and severity of central sensitization, however the equipment is expensive and therefore limited to specialized (chronic) pain clinics. Moreover, it is the goal of the present mechanism based clinical guidelines to alert manual therapists to recognize central sensitization in individual cases with musculoskeletal pain without the use of such equipment.

Heightened bilateral responses to the brachial plexus provocation tests have been proposed as a sign of central sensitization in patients with chronic whiplash associated disorders (Sterling and Kenardy, 2008). Like every other tissue in the human body, peripheral nerves and nervous tissues (including connective tissue) themselves can become hypersensitive to mechanical stimuli such as tension and pressure. Pain provocation during neurodynamic testing is a stable phenomenon and the range of elbow extension corresponding with the moment of 'pain onset' and 'submaximal pain' can be measured reliably (Coppieters et al., 2002). A bilateral loss of elbow extension that is $\geq$30°, which is also associated with moderate reports of pain when testing is taken to the pain threshold might indicate central hyperexcitability in patients post-whiplash (Sterling and Kenardy, 2008). Again, this should be interpreted together with the other signs and symptoms of central sensitization. It should not be viewed as a unique sign indicating central sensitization. Likewise, increased sensitivity of muscle and joint tissue to pressure and tension can be assessed using muscle and joint end feel testing.

Besides the passive tests listed above (Table 3), altered sensory processing can be demonstrated during exercise. Pain thresholds increase during physical activity in healthy individuals and can stay augmented for up to 30 min post-exercise. This is the result of endogenous opioid release (Koltyn and Arbogast, 1998) and related activation of several (supra)spinal anti-nociceptive mechanisms such as the adrenergic and serotonergic pathways (Millan, 2002). In certain chronic pain populations, these anti-nociceptive mechanisms appear unable to respond to a variety of stressors, including the exercise trigger (Whiteside et al., 2004; Staud et al., 2005). In subjects with chronic low back pain, pain thresholds increase normally in response to exercise (Hoffman et al., 2005), indicating the inability to generalize the finding of deregulated anti-nociceptive mechanisms during exercise to all chronic pain populations. Increased pain perception in response to exercise could be indicative of a deregulated anti-nociceptive mechanism. Stress (particularly when chronic) may well trigger lower pain thresholds. This was demonstrated by Suarez-Roca et al. (2008) who reported reduced GABA neurotransmission and consequent hyperalgesia in rats after repeated forced swimming stress.

Table 3
Overview of the clinical examination of patients with suspected central sensitization.[a]

Clinical tests
1. Assessment of pressure pain thresholds at sites remote from the symptomatic site
2. Assessment of sensitivity to touch during manual palpation at sites remote from the symptomatic site
3. Assessment of sensitivity to vibration at sites remote from the symptomatic site
4. Assessment of sensitivity to heat at sites remote from the symptomatic site
5. Assessment of sensitivity to cold at sites remote from the symptomatic site
6. Assessment of pressure pain thresholds during and following exercise
7. Assessment of joint end feel
8. Brachial plexus provocation test

[a] For all the tests used for the assessment of central sensitization, hypersensitivity to a stimulus needs to be demonstrated at both symptomatic and distant sites (Yunus, 2007a).

The assessment of the pressure pain threshold in response to exercise represents an easily applied test. The patient is required to cycle on a stationary bike at a constant speed (Whiteside et al., 2004). The resistance is gradually increased (20–50 kW/min) from a very low starting point (10–50 kW). Pressure pain thresholds are measured every 1 or 2 min during the exercise test at an anatomically standardized location at a site distinct from the primary source of nociception (e.g. the skin web between thumb and index finger in patients with chronic low back pain). The test is terminated as soon as the pattern of pain threshold change (decrease, increase or no change) becomes apparent and prior to the onset of lower leg muscle soreness or the point where post-exertional malaise may be triggered. In the case of the normal functioning of central anti-nociceptive mechanisms, a gradual increase in the pain threshold during and following exercise is observed (Koltyn and Arbogast, 1998; Whiteside et al., 2004). A constant or decreased pain threshold during and following exercise suggests malfunctioning of these anti-nociceptive mechanisms (Whiteside et al., 2004) and hence central sensitization. An abnormal pain threshold response to exercise should be regarded as one of the many possible signs of central sensitization. If present, it means that the patient can become increasingly susceptible to all kinds of nociceptive stimuli during exercise (interventions), which to a further extent may be indicative of general stress loading intolerance. Caution is required when applying exercise or activity interventions to such patients, especially when applying time contingent exercise interventions as is usually the case with graded exercise therapy programs (Nijs et al., 2009).

5. Analyzing the treatment response to recognize central sensitization

In some cases of musculoskeletal pain, the process of central sensitization is not present at the time of treatment initiation, but

becomes apparent during the rehabilitation process. This is most often the case when physical and emotional stressors combine, resulting in an overall load that is beyond the load tolerance of the individual patient. One should be aware that manual therapy aims at increasing the patient's load tolerance, but on the other hand the therapy itself can be a stressor as well. The signs and symptoms listed above can provide manual therapists with important clues for alterations in central sensory processing that can take place during the transition from acute to chronic pain. In addition to the appearance of new symptoms during the treatment course, existing symptoms may aggravate and expand, even to sites outside and remote from the symptomatic site. In case of the latter, manual therapists are well trained to differentiate referred sensations from new onset symptoms. Other factors that relate to the treatment response (non-responders, post-exertional malaise, decreased pain threshold during hands-on treatment) may point towards deficient central processing of nociception, as discussed below.

Data are available suggesting that the presence of sensory hypersensitivity influences outcome in physical rehabilitation for patients with chronic whiplash associated disorders (Jull et al., 2007). Those patients having both widespread cold and mechanical hyperalgesia showed least improvement. Certainly not all cases of unsuccessful treatment responses fall within the category of central sensitization, but some do. Manual therapists are recommended to consider the possibility of central sensitization in cases of poor treatment progress. The report of a strong increase in symptom severity post-treatment represents another sign possibly pointing towards central sensitization. Manual therapists may trigger symptom increases when applying too vigorous exercises or aggressive hands-on therapy, such as high velocity joint manipulation. Further aggressive forms of myofascial treatment such as ischemic compression could further accelerate the process of central sensitization (Nijs and Van Houdenhove, 2009; Nijs et al., 2009). Even during treatment, the patient with central sensitization may respond differently: if central sensitization is present then pain thresholds may further decrease during the use of high-intensity hands-on treatment. This is a clinical sign of the inability of the descending anti-nociceptive pathways to suppress temporal summation or wind-up in patients with central sensitization. As explained above, the reporting of strong increases in symptoms in response to low to moderate exercise therapy (i.e. in the context of post-exertional malaise) may point towards impaired anti-nociceptive mechanisms during exercise.

Table 4
Summary guide for clinicians.

	Key clinical messages
1	CS is frequently present in various chronic musculoskeletal pain disorders (listed in Table 1)
2	The clinical picture of CS is suggestive of a general load intolerance to all kinds of physical and emotional stressors and hence a large decreased load tolerance
3	To recognize CS, question the patient for hypersensitivity to touch, bright light, sound, smell, hot or cold sensations, mechanical loading of musculoskeletal tissues, and all kinds of physical, mental and emotional stressors (Table 2)
4	In case of CS, hypersensitivity is widespread rather than local (segmental)
5	Clinical tests assessing nociceptive processing may be used to recognize CS, to assess the severity of CS, to examine the treatment response and to determine the appropriate treatment parameters of manual therapy skills
6	The appearance of new symptoms during the treatment course, aggravation of existing symptoms, not responding to established treatments, post-exertional malaise, or a decreased pain threshold during hands-on treatment might indicate a developing or progressive CS

CS, central sensitization.

6. Conclusion

By using our current understanding of central sensitization during the clinical assessment of patients with musculoskeletal pain, manual therapists can apply the pure science of nociceptive and pain neurophysiology to the practice of manual therapy. The diagnosis of central sensitization in individual patients with musculoskeletal pain is not straightforward, however manual therapists can use information obtained from the medical diagnosis, history taking of the patient, clinical examination, and the analysis of the treatment response to recognize central sensitization (a summary guide is presented in Table 4). The outcome of the diagnostic process can be used to determine the appropriate treatment parameters (e.g. intensity and frequency of various manual therapy techniques). The guidelines presented here require large scale testing in clinical populations to generate clear-cut diagnostic decision trees (in line with the one presented in Fig. 2).

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