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Assessment and manifestation of central sensitisation across different chronic pain conditions

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Abstract

Different neuroplastic processes can occur along the nociceptive pathways and may be important in the transition from acute to chronic pain and for diagnosis and development of optimal management strategies. The neuroplastic processes may result in gain (sensitisation) or loss (desensitisation) of function in relation to the incoming nociceptive signals. Such processes play important roles in chronic pain, and although the clinical manifestations differ across condition processes, they share some common mechanistic features. The fundamental understanding and quantitative assessment of particularly some of the central sensitisation mechanisms can be translated from preclinical studies into the clinic. The clinical perspectives are implementation of such novel information into diagnostics, mechanistic phenotyping, prevention, personalised treatment, and drug development. The aims of this paper are to introduce and discuss (1) some common fundamental central pain mechanisms, (2) how they may translate into the clinical signs and symptoms across different chronic pain conditions, (3) how to evaluate gain and loss of function using quantitative pain assessment tools, and (4) the implications for optimising prevention and management of pain. The chronic pain conditions selected for the paper are neuropathic pain in general, musculoskeletal pain (chronic low back pain and osteoarthritic pain in particular), and visceral pain (irritable bowel syndrome in particular). The translational mechanisms addressed are local and widespread sensitisation, central summation, and descending pain modulation.

Significance: Central sensitisation is an important manifestation involved in many different chronic pain conditions. Central sensitisation can be different to assess and evaluate as the manifestations vary from pain condition to pain condition. Understanding central sensitisation may promote better profiling and diagnosis of pain patients and development of new regimes for mechanism based therapy. Some of the mechanisms underlying central sensitisation can be translated from

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animals to humans providing new options in development of therapies and profiling drugs under development.

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1. Introduction

The prevalence of moderate to severe, chronic non-malignant pain has been estimated at approximately 19% (Reid et al., 2011; Kennedy et al., 2014). Due to demographic and lifestyle changes the prevalence of chronic pain is expected to further increase in the future.

It is evident that chronic pain represents a substantial worldwide socio-economical problem (Breivik et al., 2006; Tsang et al., 2008; Johannes et al., 2010; Reid et al., 2011), and the lost productivity contributes to a high economic burden (Gaskin and Richard, 2012; Leadley et al., 2012). Indeed, pain disorders are amongst the most prevalent, costly, disabling and commonly researched conditions in the workplace (Schultz et al., 2007).

For the individual patient, chronic pain is associated with a negative impact on the overall quality of life, including physical and emotional well-being, sleep quality, and functional status (Menefee et al., 2000; Breivik et al., 2006; Fine, 2011), leading to massive psychosocial implications (Vartiainen et al., 2016) and increased incidence of depression (Munce and Stewart, 2007). It is estimated that a 60-year old woman with osteoarthritis (OA) has lived 30% of her life with impaired function and pain (Vos et al., 2012). Furthermore, severe chronic pain can shorten the life expectancy (Torrance et al., 2010).

As there is often a disparity between the chronic pain intensity and the severity of the tissue damage (e.g. extent of nerve trauma, degree of joint damage, size of gastric ulcer, extent of endometriosis), health care professionals tend to underestimate the pain intensity as compared to what is actually reported by the patients (Puntillo et al., 2003). One reason for this disparity and the un-proportionally high pain experience is most likely various sensitisation processes and in particular the facilitated central gain (i.e. amplification of central excitatory signalling).

The continuous flow of new fundamental knowledge about central nociceptive processes has to some degree been translated into the clinic and has enhanced the understanding of the various signs and symptoms across pain conditions. At the same time, it has also generated some misconceptions. As sensitisation phenomena are readily recognised across neuropathic pain conditions, the central sensitisation features have often been interchanged with the neuropathic pain terminology and caused some confusion.

The aims of this paper are to introduce and discuss (1) some common fundamental central pain mechanisms, (2) how they may translate into the clinical signs and symptoms (neuropathic pain vs. central sensitisation) across different chronic pain conditions, (3) how to evaluate gain and loss of function using quantitative pain assessment tools, and (4) the implications for optimising prevention and management of pain.

The chronic pain conditions selected for the paper are neuropathic pain in general, musculoskeletal pain (chronic low back pain and osteoarthritic pain in particular), and visceral pain (irritable bowed syndrome in particular). The translational mechanisms addressed are local and widespread sensitisation, central summation, and descending pain modulation.

2. Defining and assessing sensitisation

According to the International Association for the Study of Pain (IASP the definition of central sensitisation is, 'Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input' (taxonomy is available from http://www.iasp-pain.org/Taxonomy#Sensitisation).

As direct electrophysiological recordings from central neurons are not an option in humans, the term 'central sensitisation' should therefore be used cautiously in humans.

In addition, the term may for many purposes be a too broad term from a mechanistic point of view as 'central' may refer to (1) ipsilateral sensitisation associated with the local nociceptive focus, (2) segmental sensitisation contralateral to the local nociceptive focus, (3) extraterritorial spreading sensitisation around local nociceptive focus, or (4) generalised widespread sensitisation. A recent review has in details discussed the various mechanisms underlying spreading of sensitisation and the associated terminology (Arendt-Nielsen et al., 2014b), and when possible the specific terms defined above will in the present paper. The terminology 'central sensitisation' (CS) will be used and will encounter both segmental and extrasegmental spreading sensitisation.

Clinically a variety of diagnostic surrogate markers, besides clinical history (e.g. intensity, character/modality, spatial and temporal characteristics, spontaneous/provoked, and possible exacerbating factors of the pain), are being used for assessment including questionnaires (e.g. neuropathic pain scales and pain features), simple bedside sensory testing (hypo- or hyper-phenomena, wind-up like pain and after-sensation), and mapping of areas with sensory abnormalities.

In more research-based environments experimental mechanistic sensitisation proxies have been developed to estimate the nociceptive excitability of the nervous system. By combining different quantitative assessment tools, it is possible to get an estimate of how the peripheral and central nervous system are functioning (gain or loss of functions). Quantitative sensory testing (QST) is a way to evaluate the excitability of different pain pathways/mechanisms and involves a variety of stimulus modalities (thermal, mechanical, chemical, electrical), assessment methods (psychophysics (thresholds, ratings), electrophysiology, imaging), and structures (skin, muscles, joint, and viscera).

QST can provide an understanding of aspects related to pain transduction, transmission, and perception under normal and pathophysiological conditions and hopefully in the future provide mechanism-based diagnosis, prevention, and management of pain (Jensen and Baron, 2003). Different QST protocols have been suggested for profiling patients, and the QST battery developed by the German Research Network on Neuropathic Pain (DFNS) is the one applied in most studies with focus on neuropathic pain condition (Magerl et al., 2010; Maier et al., 2010; Geber et al., 2011). In QST studies, the focus and mind-set are often directed towards hyperexcitable responses, but as pointed out by DFNS, it is important to focus both on 'gain-of-function' and on 'loss-of-function' as hypoalgesia can also be a prominent sign in neuropathic pain (Jensen and Baron, 2003; Haanpaa et al., 2011).

The DFNS protocol assesses the function of small (thermal thresholds) and large (tactile and vibration thresholds) nerve fibre pathways and increased/decreased pain sensitivity (hyperalgesia, allodynia, hyperpathia, wind-up like pain). Hence, the battery consists predominantly of cutaneous stimulus modalities and is therefore less adequate for profiling musculoskeletal or visceral pain conditions.

The currently suggested test platforms for assessing neuropathic pain (e.g. Maier et al., 2010), musculoskeletal pain (Arendt-Nielsen et al., 2015a), and visceral pain (Brock et al., 2009) all have their different limitations: Most likely a common sensory test platform cannot be developed as the manifestations to be assessed vary between the different types of conditions. However, this review will emphasise that some dynamic sensory tests may act as general proxies for CS (e.g. central temporal summation and descending pain modulation) across conditions.

Besides, standard clinical and sensory testing, neuroimaging (e.g. Alomar and Bakhaidar, 2016; Morton et al., 2016) and electrophysiological (Lelic et al., 2014; Pinheiro et al., 2016) assessments have been suggested as tools for evaluating sensitisation processes, but these options are not further discussed in the present paper.

3. Neuropathic pain versus central sensitisation

In the literature, there is a general trend to interchange neuropathic pain symptoms and CS. However, neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system (Jensen et al., 2011).

It can be debated which somatic painful disorders besides neuropathy could qualify for this definition; e.g. what is the evidence that osteoarthritis includes neuropathic lesions, what is the evidence that idiopathic chronic low back pain (LBP) without radiculopathy includes damage of the nervous system, and what is the evidence that, e.g. irritable bowel disorders and fibromyalgia involve nervous system damage or disease?

In the present paper, we use the terminologies (1) neuropathic pain for disorders with validated nerve damage and (2) CS when it can be assessed by specific experimental proxies (e.g. widespread hyperalgesia, temporal summation, descending inhibition) and can be applied across different chronic pain conditions.

It has recently been argued that the many 'functional', 'dysfunctional', and 'idiopathic' types of chronic pain conditions (e.g. fibromyalgia, complex regional pain syndrome type 1, 'nonspecific' chronic low-back pain, whiplash, irritable bowel syndrome, painful bladder syndrome) should be integrated into a new chronic pain ICD11 classification (Treede et al., 2015), and the term for such a common descriptor is currently being discussed (Kosek et al., 2016).

4. Assessing sensitisation: peripheral versus central

One aspect to address is the challenge of separating peripheral versus central manifestations of sensitisation.

If a given non-painful or painful stimulus is applied to a patient, it can be difficult to determine if the assessed reaction is a result of localised sensitisation/desensitisation or caused by a generalised increase/decrease in sensitivity. Recently, topographical pain sensitivity mapping techniques based on many consecutive assessments in a restricted area have been developed to assess pain thresholds over an area, e.g. a nerve innervation territory (de la Llave-Rincon et al., 2009), oral cavity (Lu et al., 2013), joint structure (Arendt-Nielsen et al., 2015a), muscle/tendon structures (Fernandez-de-Las-Penas et al., 2009; Fernandez-Carnero et al., 2010), or visceral location (Drewes et al., 1997) and specific areas of sensory abnormalities can be determined. The topographical mapping technique provides an opportunity to determine local spots with specifically changed pain sensitivity (e.g. tender spots, tendon-muscle interaction) which obviously in addition to the local changes will be affected by a general increase in central gain.

Assessing the sensory abnormalities from specific structures require different stimulators/activators. Cutaneous stimulation with pin-prick or heat is easy, whereas activating deeper structures such as muscles, tendons, bones, joints, or viscera is more challenging. In recent years, new developments have predominantly focused on these latter structures due to their clinical relevance and the increased focus on sensitisation associated with these structures (for reviews see Arendt-Nielsen and Yarnitsky, 2009; Drewes et al., 2003).

To estimate the contribution of peripheral sensitisation a minimum of two locations from two different segmental levels should be assessed and compared with a pain-free population (normative database). If generalised sensitisation is present in a given patient, all thresholds or pain ratings (assessed locally and distantly to injury) will be affected, and hence the comparison with pain free volunteers will provide information of the relative peripheral and central contribution If CS is restricted to the segmental level of the nociceptive focus, the extrasegmental site may not differ from controls (Fig. 1).

4.1 Clinical assessment of central sensitisation

Clinical and experimental characteristics of CS are observed across many different chronic pain conditions (Julien et al., 2005; Campbell and Meyer, 2006; Drewes et al., 2006; Veves et al., 2008; Woolf, 2011; Nijs et al., 2014; Fingleton et al., 2015).

It has been claimed that CS is most pronounced in pain conditions with a neuropathic component (Freynhagen and Baron, 2009; Woolf, 2011). However, this is difficult to validate since there is no applicable definition, method, or guideline for diagnosing CS.

Pain Sensitivity Questionnaire (PSQ) and the Central Sensitivity Index (CSI), have been developed (Ruscheweyh et al., 2009; Mayer et al., 2012; Nijs et al., 2014) to assess various aspects of the clinical pain perceived. Significant correlations have been observed between PSQ scores and pain intensity

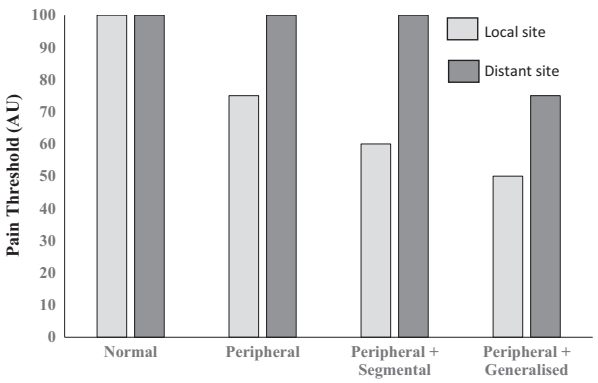

Figure 1 A schematic illustration of how the different sensitisation processes may contribute to the assessed pain reaction (pain threshold). The assessments of thresholds from two locations in a normal healty volunteers are assigned 100%. In a pain patient with only localised, peripheral sensitisation the threshold from the affected region (local site) is reduced. The assessment from a distant, normal site is similar to a healthy control. In a patient with peripheral as well as segmental sensitisation the threshold is further reduced whereas the extrasegmental site may be normal. In case of generalised sensitisation the local threshold is further reduced at the local site but also reduced at the distant, extrasegmental site. Statistical compararison with a healthy, normal, pain free population is the only way to evaluate the degree of localised and spreading sensitisation in a given patient or patient population.

ratings (Ruscheweyh et al., 2009; Sellers et al., 2013) but possible associations to CS as assessed by experimental measures have not yet been established.

The painDETECT questionnaire has been developed as a neuropathic screening tool for assessing neuropathic components in chronic musculoskeletal pain, such as chronic LBP (Freynhagen et al., 2006) and OA (Hochman et al., 2013), but it is not specifically useful for neuropathic pain conditions with sensory loss (Vollert et al., 2016). More recently another mechanism-based classification questionnaire has been developed for LBP to identify symptoms and signs associated with a clinical classification of CS in patients with low back (± leg) pain (Smart et al., 2012). Clinical mapping of pain areas, referred pain areas, or areas with sensory hypo-/hypersensitivity is useful for understanding if a given condition is restricted to a neuronal territory or spreading across territories/segments. Furthermore, the development of such areas can be followed quantitatively over time and normally expansions are indicative of increased central involvement. Area expansions and perceptual changes into a more diffuse character of the pain are observed in patients developing additional painful comorbidities (Thompson et al., 2010). The areas can be digitally scanned and the area calculated.

4.2 Experimental assessment of central sensitisation

There is ample preclinical (Tal and Bennett, 1994; Malan et al., 2000), human experimental (Shenker et al., 2008), and clinical (Konopka et al., 2012) evidence that for neuropathic-like conditions the signs and symptoms (sensory abnormalities) can extend into regions beyond those directly innervated by the injured nerve. This emphasises that there may be no non-affected control site in a chronic pain patient.

In the following specific quantitative experimental tools for assessing CS will be discussed.

4.2.1 Widespread sensitisation

Many clinical QST studies have shown this widespread sensitisation not only in case of neuronal injuries, but also found in conditions like migraine and chronic tension type headache (Fernandez-de-Las-Penas et al., 2010).

Similarly, contralateral and extrasegmental widespread pressure pain hyperalgesia are found in, e.g. patients with painful knee OA (Arendt-Nielsen et al., 2015a), unilateral epicondylitis (Fernandez-Carnero et al., 2009), and chronic visceral pain conditions (Giamberardino, 2003; Bouwense et al., 2013).

The only way to overcome the problem with lack of control points in pain patients widespread hyperalgesia is to use normative databases from sex and age matched controls (Neziri et al., 2011). A given assessment from a patient can then be compared with controls in the database using *Z*-scores to judge if an individual patient has a sensory abnormality (Rolke et al., 2006; Pfau et al., 2014).

4.2.2 Wind-up like pain (temporal summation) and after-discharge

The wind-up process measured from dorsal horn wide-dynamic range neurons in animals is a progressive increase in neuronal output during the course of a train of identical afferent nociceptive stimuli (homosynaptic potentiation). This repeated high intensity afferent barrage will cause the increased neuronal output to last after the end of the repeated stimuli and CS has been generated. In humans, psychological or electrophysiological (facilitated reflexes) responses are used as proxies for the initial part of the wind-up process. This phase translates into the so-called temporal summation. If a painful stimulus is repeated 1–3 times per second for 5 to 10 s, the pain will integrate and become more painful at the end of the stimulus train (Arendt-Nielsen et al., 1994). Facilitation of temporal summation is considered a measure of increased central gain of pain, and temporal summation is a very powerful mechanism difficult to block with conventional analgesics or anaesthetic procedures (Petersen-Felix et al., 1996).

Temporal summation can be elicited using electrical, mechanical or thermal stimulation modalities and can be elicited from the skin, musculoskeletal structures, and viscera (Arendt-Nielsen, 1997; Arendt-Nielsen and Yarnitsky, 2009).

In clinical bedside testing, simple devices are used for assessing temporal cutaneous summation such as tapping the skin with a nylon filament (Nikolajsen et al., 1996). However, when more standardisation is required, automated user-independent methods are needed such as thermal (Kong et al., 2013), pressure (Nie et al., 2009), or electrical stimulation techniques of the skin (Arendt-Nielsen et al., 1994), muscles (Arendt-Nielsen et al., 1997b; Skou et al., 2013), and viscera (Drewes et al., 1999).

In many chronic pain conditions, such as neuropathic (Nikolajsen et al., 1996; Maier et al., 2010), musculoskeletal (Staud et al., 2014; Tesarz et al.,

2016), joint (Arendt-Nielsen, 2017), and visceral pain (Arendt-Nielsen, 1997; Dimcevski et al., 2007; Sherman et al., 2015), the temporal summation is significantly facilitated.

Sometimes pain patients experience painful aftersensations when the train of repeated stimuli has stopped (Robinson et al., 2010), and the duration of this phenomenon is prolonged in tension-type headache/temporomandibular pain patients as compared with controls (Sato et al., 2012). This has also been observed in patients with neuropathic (Gottrup et al., 2003) or musculoskeletal chronic pain (Staud et al., 2003, 2007).

4.2.3 Spatial summation

Nociceptive stimuli do not only integrate temporally, but also spatially (Quevedo and Coghill, 2007). Spatial summation is an increase in pain intensity when the size of the stimulated area is expanded, e.g. if the number of stimulation probes delivering a painful heat stimulus is increased from 1 to 5 (Nielsen and Arendt-Nielsen, 1998). Spatial integration relies on central networks and the general sensitisation status (Bouhassira et al., 1995).

In humans, spatial summation can be assessed in different ways applying the stimulus to different area sizes by, e.g. thermodes (Price et al., 1989; Coghill et al., 1993; Nielsen and Arendt-Nielsen, 1997), pressure probes (Greenspan et al., 1997; Nie et al., 2009), or cuffs (Polianskis et al., 2002).

Spatial summation is facilitated in various pain conditions, such as fibromyalgia (Staud et al., 2004, 2007), OA (Graven-Nielsen et al., 2012), and lateral epicondylitis (Jespersen et al., 2013). Facilitation of spatial summation is likewise considered as a measure of increased central gain of pain.

4.2.4 Descending pain modulation (conditioning pain modulation)

Descending pain inhibition is largely mediated by noradrenaline release in the spinal cord where one mechanism is noradrenaline modulation acting at the α_2-adrenoceptors and hence inhibiting the release of excitatory neurotransmitters (D'Mello and Dickenson, 2008). One aspect of the descending pain control is associated with diffuse noxious inhibitory control (DNIC), expressed as an inhibition of dorsal horn neurons along the neuroaxis as produced by a noxious stimulus applied to a body region remote from the receptive field of the neurons (Le Bars et al., 1979; Lee et al., 2011c). The endogenous descending pain control network is important for the chronification of pain (Miranda et al., 2015).

Preclinical data indicate that not only nociceptive inhibition but also descending facilitation are important for maintaining neuropathic (Wang et al., 2013; Ossipov et al., 2014) and inflammatory hyperexcitable stages (Ambriz-Tututi et al., 2011; Bannister and Dickenson, 2016). Tools to separate the two mechanisms in patients would be an important achievement.

It is generally accepted that impaired descending pain modulatory pathways and particularly the facilitatory pathways may contribute to development and maintenance of CS (Wang et al., 2013; Ossipov et al., 2014; Bannister and Dickenson, 2016) and therefore most likely are also important for clinical pain conditions (Voscopoulos and Lema, 2010). Descending pain control is known to be mediated by the descending inhibitory noradrenergic pathway and is accompanied by e.g. a gain in the descending 5HT3 receptor mediated facilitations (Bannister and Dickenson, 2016).

In humans, the assessment of the descending pathways is named conditioning pain modulation (CPM) (Yarnitsky et al., 2010). The literature on CPM in chronic pain has recently been reviewed (Lewis et al., 2012; Staud, 2012; Goubert et al., 2015).

The CPM assessment paradigm in humans can quantify the balance and hence the net sum between the inhibition and facilitation. When pain patients have impaired CPM, it is not obvious if the inhibition is reduced or the facilitation is increased, but it has been shown in chronic pain patients that the degree of widespread hyperalgesia and reduced CPM are associated (Schliessbach et al., 2013).

The CPM procedure generally shows a large variability in healthy volunteers as well as in patients, and it has recently been suggested that patients may be classified as CPM reducers (pain inhibition) or CPM increasers (pain facilitation). This may provide new insights on how to separate the two descending pathways (Potvin and Marchand, 2016).

A cohort study including 2199 healthy volunteers showed the natural Gaussian distribution of CPM responses, and it is speculated that those in the lower quartile could be more vulnerable to develop chronic pain than those in the upper quartile with a more protective CPM system (Skovbjerg et al., 2016).

Impaired CPM has been reported in many clinical conditions, such as e.g. myofascial temporomandibular joint pain (Bragdon et al., 2002), chronic LBP (Peters et al., 1992; Mlekusch et al., 2016), whiplash

(Daenen et al., 2013, 2014; De Kooning et al., 2015), long-standing patellofemoral pain (Rathleff et al., 2016), myofascial pain (Hilgenberg-Sydney et al., 2016), fibromyalgia (Kosek and Hansson, 1997; Staud, 2009), painful knee OA (Arendt-Nielsen et al., 2010), chronic LBP (Correa et al., 2015), frequent episodic tension-type headache (Drummond and Knudsen, 2011), chronic tension-type headaches (Sandrini et al., 2006), chronic daily headache (Hilgenberg-Sydney et al., 2016), endotoxemia (Karshikoff et al., 2015), interstitial cystitis (Ness et al., 2014), irritable bowel syndrome (Wilder-Smith and Robert-Yap, 2007; Williams et al., 2013), and chronic pancreatitis (Olesen et al., 2010).

In the area of neuropathic pain, several conditions have shown deficient CPM such as painful peripheral neuropathy (Niesters et al., 2013), complex-regional pain syndrome (Seifert et al., 2009), and painful diabetic neuropathy (Niesters et al., 2014).

Several chronic pain studies have shown that mainly females have deficient CPM (Karshikoff et al., 2015; Hilgenberg-Sydney et al., 2016), and hence the CPM is most reliably (test–retest) assessed in chronic pain male patients (Martel et al., 2013). In addition, race seems to affect the CPM effect (Morris et al., 2015).

The CPM deficit has been shown to correlate with the severity in patients with spinal cord injury neuropathic pain (Albu et al., 2015) where the CPM deficit correlates positively with the number of painful body regions (Gruener et al., 2016), painful chemotherapy-induced polyneuropathy (Nahman-Averbuch et al., 2011), complex-regional pain syndrome (Seifert et al., 2009), postherpetic neuralgia (Pickering et al., 2014), and traumatic peripheral nerve injury (Bouhassira et al., 2003).

Furthermore, it is important to note that the CPM efficacy declines with age (Riley et al., 2010; Grashorn et al., 2013) and is influenced by gender (Martel et al., 2013). In case that the control material consists of younger subjects, this may bias many chronic pain studies as the populations are normally middle-aged or elderly.

As such it seems that other supra-spinal or even spinal mechanisms than nociceptive may influence the CPM efficacy conditions like depressive disorders or psychosocial factors (Nahman-Averbuch et al., 2016) and hence it cannot be ruled out that some 'CPM' studies actually investigate pure cerebral processes.

This may explain why psychiatric and psychological disorders may show signs of sensitisation without any obvious peripheral drivers. This is an important area to further explore as attenuated central pain control mechanisms (most likely descending facilitatory pathways) are involved (Arendt-Nielsen et al., 2012b).

Two possible explanations can be suggested for this restoring CPM.

(1) Removing the peripheral drive
(2) Pharmacologically target neurotransmitters/-receptors boosting descending inhibition or reducing descending facilitation

During surgery, e.g. joint replacement, the peripheral nociceptive drive can be removed, and if the patient becomes pain-free, the CPM is normalised (Graven-Nielsen et al., 2012).

In chronic pain patients in whom the peripheral drive cannot be removed or inhibited a pharmacological intervention may be an option to normalise CPM (Arendt-Nielsen and Yarnitsky, 2009).

The importance of the status of the monoaminergic system for the CPM efficacy has been suggested and associations have been found between plasma-bound norepinephrine and metanephrine concentrations and the efficacy of CPM, but this effect was not observed for cerebrospinal fluid (Parent et al., 2015). Similarly, in a non-placebo controlled study the effect of duloxetine (serotonin-norepinephrine reuptake inhibitor) was found to be highest in those painful diabetic neuropathic patients with the most impaired CPM (Yarnitsky et al., 2012). Furthermore, drugs with effect on the opioid and noradrenergic system, such as tapentadol, seem to facilitate CPM (Niesters et al., 2014). The dopaminergic system has also been suggested to play a role for the potency of CPM (Treister et al., 2013) and polymorphisms in serotonin and dopamine-related gene regulation are found to affect endogenous pain modulation (Treister et al., 2011).

5. Clinical evidence for central sensitisation: examples of neuropathic, musculoskeletal, joint, and visceral pain conditions

Clinical characteristics indicative of CS are observed in many chronic pain conditions (Julien et al., 2005; Campbell and Meyer, 2006; Drewes et al., 2006; Veves et al., 2008; Woolf, 2011; Fingleton et al., 2015; Arendt-Nielsen, 2017), but no definitive method of diagnosing CS is currently available (Nijs et al., 2014). Thus, CS cannot be excluded as a contributing factor to any type of chronic pain, and specific estimates of the prevalence of CS in chronic

pain patients are generally lacking. Nevertheless, the prevalence of CS has been estimated based on the presence of certain clinical characteristics, including symptoms typical of neuropathic pain. In a 2014 systematic review by Lluch and colleagues, 28 to 34% of patients with OA knee pain were estimated to have CS, but this was based on the reported presence of neuropathic pain symptoms which is not a definition of CS (Lluch et al., 2014).

One important limitation is that there are no longitudinal studies following the development of CS over time but only cross-sectional studies on patients with different duration and intensity of their chronic pain. Although we know that sensitisation can be induced very quickly in the laboratory after, e.g. intradermal capsaicin injection (Iannetti et al., 2013) and resolved very quickly in the clinic when blocking the peripheral drive maintaining CS (Gracely et al., 1992), it could be assumed that it may also develop quickly in a clinical context if a sufficient peripheral nociceptive barrage is initiated momentarily (except in an acute post-operative setting). However, in many clinical conditions the pain develops slowly over time and consequently it takes a while before the nociceptive drive reaches a sufficient level to initiate and maintain the sensitisation.

The following sections will provide a brief preclinical introduction highlighting the most fundamental findings relevant for CS in relation to the chronic pain conditions addressed (neuropathic, musculoskeletal (chronic LBP), joint specific (osteoarthritis), and visceral (irritable bowel syndrome)). This will be followed by presenting the individual manifestations of signs and symptoms, a discussion in the context of CS, and its assessment focusing on the introduced tools.

5.1 Neuropathic pain

A main problem in developing new drugs for treating neuropathic pain is the lack of translation from animal data into clinic (Percie du Sert and Rice, 2014). Preclinical 'models of neuropathic pain' should be developed to reflect more closely the pathophysiological conditions found in humans.

From preclinical data it is evident that CS can occur at segmental and extra-segmental levels with exaggerated pain response, spreading hyperalgesia, and allodynia (Baron, 2006).

However, a main problem is that many animal models of neuropathic pain often focus on one nerve (sciatica) and assess hyperalgesia/allodynia but do not address the spontaneous nociceptive behaviour as spontaneous pain is the main problem for the patients. There is firm evidence that CS is present in animal models of nerve damage.

5.1.1 Localised and widespread hyperalgesia

The response to intradermal capsaicin has been investigated in the painful and non-painful legs of patients with unilateral sciatica and compared with healthy controls. Pain and hyperalgesia responses were enhanced in both legs of patients with unilateral sciatica compared with healthy controls supporting the notion that patients with pre-existing neuropathic pain have fundamental differences in the central nervous system processing compared with pain-free controls (Aykanat et al., 2012). There is ample clinical evidence that in neuropathic conditions the signs and symptoms extend into regions beyond those directly innervated by the injured nerve (Malan et al., 2000; Konopka et al., 2012).

Contrary to many of the above findings for postherpetic neuralgia (PHN) the pain remains localised with no contralateral effects on neurogenic inflammation (Baron and Saguer, 1994) or facilitated capsaicin provoked pain (Petersen et al., 2000) suggesting PHN as a specific class of neuropathic pain.

Use of the standardised QST protocol of the German Research Network on Neuropathic Pain has revealed abnormality for some sensory parameters at the non-affected side that was as high as 57%; this indicates that bilateral sensory dysfunction in patients with unilateral neuropathic pain is more the rule than the exception (Konopka et al., 2012) and often very minimal sensory differences exist between affected and non-affected areas (Geber et al., 2011). Studies of thermal sensory function at the affected and non-affected side of acute and chronic complex regional pain syndrome patients have shown bilateral sensory changes as well (Huge et al., 2008). Likewise, bilateral thermal detection and pain threshold sensitisation have been demonstrated in patients with unilateral carpal tunnel syndrome compared with controls (de la Llave-Rincon et al., 2009), and in a similar patient population bilateral pressure pain hyperalgesia was found (de la Llave-Rincon et al., 2009).

5.1.2 Temporal summation

Temporal summation (wind-up like pain) is one of the tests in the DFNS platform, and 33% of patients with neuropathic pain are found to have facilitated summation (Maier et al., 2010). The DFNS

technique is based on a handheld filament, whereas Nikolajsen et al. (1996) used an automated activator which allowed precise adjustment of the stimulation frequency (normally 2 Hz) (Nikolajsen et al., 1996).

Similarly, facilitated wind-up pain is found in postherpetic neuralgia (Eide et al., 1994) and in patients with chronic postsurgical neuropathic pain (Pud et al., 1998).

Occasionally neuropathic pain patients will experience an aftersensation after, e.g. 1 min of repeated 2 Hz stimulations (Gottrup et al., 2003).

5.1.3 Descending pain control

Patients with neuropathic pain after a spinal cord injury showed a dysfunction of CPM which correlated positively with the number of painful body regions (Gruener et al., 2016).

In recent years, a number of neuropathic pain studies have been published showing impaired descending pain control in painful neuropathies such as postherpetic neuralgia (Pickering et al., 2014) and traumatic peripheral nerve injury (Bouhassira et al., 2003).

It has even been suggested that the CPM paradigm could be useful for predicting treatment effects (Granovsky, 2013), such as the effect of duloxetine in painful diabetic neuropathy (Yarnitsky et al., 2012).

In patients with chronic radicular pain, the impaired descending inhibitory pain modulation is restored by hydromorphone (Suzan et al., 2015) and in patients with diabetic polyneuropathy a 4-week tapentadol treatment potentiated the descending pain inhibition (Niesters et al., 2014).

Thus, there is firm clinical evidence that CS is present in patients with neuropathic pain.

5.2 Low back pain

Preclinical back injury models have demonstrated that CS can be evoked (Amaya et al., 2009; Xie et al., 2012; Strong et al., 2013) and that the models elicited radiating nociceptive reactions and an increase in heat hyperalgesia in the hind paw which was outside the affected segment (Amaya et al., 2009).

The central alterations in the spinal cord using such models have shown activation of glial cells and release of cytokines comparable to those observed in other neuropathic pain models (Strong et al., 2013).

In several human and animal studies, sensory nerve fibres in degenerated discs were shown to express painful neuropeptides and growth factors, such as substance P (Ashton et al., 1994; Coppes et al., 1997) and calcitonin gene-related peptide (McCarthy et al., 1991; Roberts et al., 1995) as well as nerve growth factors (Miyagi et al., 2011). There is firm evidence that CS is present in animal models of back injury models.

5.2.1 Localised and widespread hyperalgesia

A recent study concluded that most QST measurements have acceptable reliability in patients with chronic LBP including pressure pain thresholds normally used for assessing CS (Vuilleumier et al., 2015). Furthermore, the pressure pain threshold seems to be the most sensitive to assess CS in chronic LBP (Neziri et al., 2012).

However, studies within the area of chronic LBP have provided conflicting data on whether the patients develop generalised hypo- or hyperalgesia. Naliboff et al. (1981) and Cohen et al. (1983) reported increased thresholds to radiant heat stimuli compared with pain-free controls. On the other hand, Peters et al. (1992) hypothesised higher electrical pain thresholds, but found no statistically significant group differences.

Most studies have found localised or generalised hyperalgesia in chronic LBP.

Schmidt and Brands (1986) and Brands and Schmidt (1987) reported greater pain intensity and less pain tolerance with the cold pressor test in chronic, idiopathic LBP compared with controls. On the contrary, Blumenstiel et al. (2011) concluded that LBP patients displayed significantly lower PPT in the painful area of the back but not on the dorsum of the hand suggesting only localised sensitisation.

Giesecke et al. (2004) compared chronic idiopathic LBP patients with fibromyalgia patients and healthy controls and found a general increase in pressure pain sensitivity in both patient groups. Data from Puta et al. (2012) supported the finding of generalised hyperalgesia in chronic LBP.

Similar findings of generalised pressure hyperalgesia in chronic LBP has been found in other studies (Giesbrecht and Battie, 2005; Imamura et al., 2013; Correa et al., 2015).

O'Neill and colleagues demonstrated the presence of generalised deep-tissue hyperalgesia in patients with chronic LBP and intervertebral disc herniation (O'Neill et al., 2007). The concept of facilitated central gain in chronic LBP is also supported by an EEG mapping study (Diers et al., 2007).

The nociceptive reflexes have been used to assess the central consequences of chronic LBP and were

shown to be reliable in these patients (Biurrun Manresa et al., 2011). A more advanced version of this technique is to assess the reflex-receptive fields (reflecting enlarged receptive fields of dorsal horn neurons), and facilitation of those fields has been demonstrated (Biurrun Manresa et al., 2013) to further support CS.

It has been proposed that the CS could be an important driver for the increased incidence of painful co-morbidity in chronic LBP as minimal nociceptive input from a given structure (e.g. an osteoarthritic joint) could generate pain (Hestbaek et al., 2004; Andersen et al., 2012).

5.2.2 Temporal summation

The summation threshold has shown to be reliably assessed between sessions in chronic LBP patients providing the opportunity to use this parameter for monitoring (Biurrun Manresa et al., 2011). When different QST modalities have been used to discriminate chronic LPB patients from healthy controls, the temporal summation showed good discriminability (fitted area under the receiver operating characteristic (ROC), 0.80) (Neziri et al., 2012) with a significant association with clinical pain severity and disability (Owens et al., 2016). Of note, the temporal summation was elevated in chronic LBP patients who had experienced emotional abuse during their childhood (Tesarz et al., 2016).

Most studies have used psychophysical assessments, but Biurrun Manresa et al. (2013) found facilitated temporal summation in LPB when assessed by the nociceptive withdrawal reflex.

The facilitated temporal summation in chronic LBP indicates central involvement of e.g. the NMDA receptor as supported by findings showing that magnesium administration is efficient in dampening the pain in a specific group of refractory chronic LBP patients (Yousef and Al-deeb, 2013).

5.2.3 Descending pain control

It has been debated if the CPM paradigm can provide information about the facilitatory as well as the inhibitory pathways, and it has been shown that a subgroup of chronic LBP patients showed reduced CPM and another group facilitated CPM (Rabey et al., 2015).

One of the first studies on impaired descending pain modulation in chronic LBP was published in 1992 (Peters et al., 1992), and later other studies have followed with the same result (Owens et al., 2016). Evidence has been provided that endogenous modulation is also impaired in acute LBP (Mlekusch et al., 2016) raising the question for how long the LBP should be present in order to have an impact on CPM.

Taken together, there is firm evidence that CS is present in patients with chronic LBP.

5.3 Osteoarthritis (OA) pain

A number of reviews have focused on the role of CS in preclinical joint pain models (Schaible, 2004). However, in recent years, it has been debated intensively how well the animal OA models translate into patients. Many drug trials have failed as no effects were found in patients although clear effects were found in the preclinical models.

Among the different models, intra-articular injection of monosodium iodoacetate (MIA) induces structural changes in the knee joint cartilage and meniscus. These are accompanied by changes in the expression of pain-mediating cytokines in the DRG and spinal cord which correlate with the development of hyperalgesia and allodynia (Im et al., 2010). The same model causes reduced nociceptive thresholds in the biceps femoris which neurophysiologically represents a spinal mechanism (Kelly et al., 2013). The monoiodoacetate (MIA) model also seems capable of activating spinal glial cells which may contribute to the development and maintenance of CS (Sagar et al., 2011).

Intense and prolonged nociceptive input from the OA knee joint in animals may also result in hyperexcitability of dorsal horn neurons (Martindale et al., 2007). Hence, there is firm evidence that CS is present in animal models of osteoarthritis.

5.3.1 Localised and widespread hyperalgesia

The role of CS in painful human osteoarthritis has attracted increasing attention (Akinci et al., 2016), and various attempts have been made to develop clinical (Akinci et al., 2016) and experimental measures (Arendt-Nielsen et al., 2015b).

In general, OA patients are more sensitive to various experimental painful stimuli as compared with age matched controls (Lee et al., 2011b) with 70% of knee OA patients having at least one somatosensory abnormality (Wylde et al., 2012b).

Several recent meta-analyses (Suokas et al., 2012; Fingleton et al., 2015) and reviews (Lluch et al., 2014; Arendt-Nielsen et al., 2015b; Arendt-Nielsen, 2017) have been published providing comprehensive analyses of all relevant sensory tests investigated in OA.

When comparing males and females with symptomatic knee OA, it seems that females show a higher degree of sensitisation to the various experimental pain stimuli (lower heat, cold, pressure thresholds/tolerances, greater temporal summation of pain) compared with males (Bartley et al., 2016).

A strong manifestations of CS in OA has been shown to be related to high levels of pain (Arendt-Nielsen et al., 2010; Finan et al., 2013), disability, poor quality of life (Imamura et al., 2008), increased spreading sensitisation (Skou et al., 2014a), poor outcome after total joint replacement surgery (Lundblad et al., 2008; Wylde et al., 2015), and high concentration of pro-inflammatory cytokines (Lee et al., 2011a).

The lack of associations between the pain intensity and objective radiological findings of the individual OA patient (Davis et al., 1992; Hannan et al., 2000; Neogi et al., 2009; Skou et al., 2014b) and the existence of specific OA subgroups (Finan et al., 2013; Arendt-Nielsen et al., 2014a, 2015a) are strong indications that pain facilitatory or inhibitory mechanisms are involved. It is not fully understood why some patients continue to have chronic pain after joint replacement and why others become pain free, but emerging evidence suggests that central pain mechanisms can be involved (Beswick et al., 2012; Petersen et al., 2015a,b; Wylde et al., 2015).

Assessing pain thresholds from the knee area versus a remote area will provide information about the extrasegmental spreading of sensitisation. It has been shown consistently across different research groups (Imamura et al., 2008; Arendt-Nielsen et al., 2010; Lee et al., 2011b; Graven-Nielsen et al., 2012; Wylde et al., 2012b; Kosek et al., 2013; Egsgaard et al., 2015) that spreading sensitisation is a feature in OA patients which most likely depends on the clinical pain intensity and pain duration (Arendt-Nielsen et al., 2015b). Lower pressure pain thresholds were shown to be associated with reduced function, increased disability, and poor quality of life in patients (Imamura et al., 2008; Kuni et al., 2015).

Recently studies have shown that preoperative widespread hyperalgesia is linked to the development of chronic postoperative pain following total joint replacement (Petersen et al., 2015a; Wylde et al., 2015).

Most studies within this area have been conducted on knee or hip OA, but Chiarotto et al. found a reduction in the pressure pain thresholds at all evaluated joint and adjacent muscle sites in patients with unilateral thumb carpometacarpal OA (Chiarotto et al., 2013).

5.3.2 Temporal summation

Preoperative temporal summation has been shown to predict the development of chronic postoperative pain following total knee replacement surgery in patients with OA (Petersen et al., 2015a, 2016; Izumi et al., 2017).

Facilitated temporal summation has been found in patients with pain after total knee replacement as compared with those who became pain free (Skou et al., 2014a). In addition, those patients with chronic pain after knee replacement showed even more facilitated summation as compared with OA patients prior to surgery (Skou et al., 2014a).

For simple bedside testing, temporal summation evoked by repeated mechanical punctate pain stimuli has been used in OA (Cruz-Almeida et al., 2013; Finan et al., 2013; King et al., 2013b), and the summation has shown association with the pain severity but not the radiographic severity (Neogi et al., 2015). The subgroup of OA patients with 'high knee pain and low knee radiographic grade' showed more facilitated temporal summation to punctate pain stimuli than the other groups (Finan et al., 2013).

Studies using repeated thermal stimuli are less conclusive as two studies have shown subgroup differences when assessed on the forearm (Finan et al., 2013) and at the knee (Cruz-Almeida et al., 2013). However, one study did not show any differences (King et al., 2013b). Ethnic differences have been found in the facilitation of temporal summation in patients with OA and hence should be considered as a source of variation (Goodin et al., 2014).

Repeated pressure stimuli using computer controlled algometry or cuff algometry have also shown facilitated temporal summation when assessed at the knee and on the arm/leg with an association with pain severity and duration but not with radiographic severity (Arendt-Nielsen et al., 2010, 2015a; Skou et al., 2013).

5.3.3 Descending pain control

In recent years, the function of the descending pathways in patients with musculoskeletal disorders has been in focus (Curatolo and Arendt-Nielsen, 2015). A recent study showed that OA patients with facilitated temporal summation together with impaired CPM have more pain after a joint replacement (Petersen et al., 2016). Along this line OA patients with chronic pain after knee replacement continue to have impaired descending control (Skou et al., 2013). Exercise is known to be advantageous in OA for pain management (Skou et al., 2015), and some

of this pain alleviation may be caused by a positive effect on CPM (Courtney et al., 2016).

A number of studies have found significantly impaired CPM in OA with an association to both pain intensity and pain duration (Kosek and Ordeberg, 2000; Arendt-Nielsen et al., 2010, 2015a; Egsgaard et al., 2015). Further, it has been found that the CPM is restored in patients after knee replacement where the patients became pain free (Kosek and Ordeberg, 2000; Graven-Nielsen et al., 2012). On the other hand, Finan et al. (2013) found no difference in CPM potency between different OA sub-groups and King et al. (2013b) found no differences between OA patients and controls.

Some studies have challenged the reliability of the CPM assessment due to the large inter- and intra-individual variation (Oono et al., 2011), and various attempts have been made to refine the technique (Biurrun Manresa et al., 2014). Recently the cuff algometry technique has been applied with one cuff delivering the conditioning stimulus and another cuff delivering the test stimulus (Graven-Nielsen et al., 2012; Petersen et al., 2015a).

It has been suggested that the impaired CPM in OA is associated with intracortical disinhibition (Tarrago et al., 2016).

Taken together, there is firm evidence that CS is present in patients with painful OA.

5.4 Irritable bowel syndrome

Irritable bowel syndrome (IBS) was selected as a visceral pain condition with indications of pronounced CS. The condition shares similarities with other functional pain conditions, such as e.g. fibromyalgia, whiplash, and endometriosis (Fig. 2).

Perturbations in visceral sensation commonly characterised by heightened sensitivity to experimental stimulation or physiological events are considered to be an important pathophysiological facet of IBS (Farmer and Aziz, 2009). IBS comprises 50% of referrals to gastroenterologists and affects up to 20% of the US population (Sandler, 1990) and for many years it has been suggested that CS is an important feature of IBS (Moshiree et al., 2006). About 80% of the patients are female and accordingly females with IBS show a greater sensitivity than matched males to rectal distension (Mayer et al., 1999; Chang et al., 2006).

IBS patients exhibit a wide variety of extraintestinal symptoms (back pain, migraine headaches, heartburn, dyspareunia, and muscle pain), which support the central pain facilitation (Whorwell et al., 1986; Mayer and Raybould, 1990). Furthermore, IBS is frequently occurring together with other disorders involving CS (Whitehead et al., 2002). Abnormal size and localisation of the referred pain area has bene used as a proxy for CS and reorganisation in patients with functional pain disorders (Mertz et al., 1998).

A variety of acute and chronic experimental stressors coupled with various assessment approaches have been used to mimic visceral pain conditions. Delivered at different phases of the life cycle, such stressors may trigger risk factors for visceral hypersensitivity. Accumulating evidence suggests that the internal and external validity of such models is adequate particularly with regard to species, specific gender, age and strain (Larauche et al., 2011; Qin et al., 2011). In contrast to human studies, in which self-reported responses to gut distension can be measured, pseudoaffective markers of the nociception in animal studies are needed. The most frequently used marker is that of contractions of the abdominal wall musculature of the animals, or visceromotor responses, to isobaric colorectal distensions (Christianson and Gebhart, 2007).

Animal models of IBS are lacking, but various gastrointestinal stressors have shown that CS can be generated.

5.4.1 Localised and widespread hyperalgesia

Initially, it was assumed that the enhanced sensitivity was limited to the gut, and over the years many studies have shown local colon or rectal hyperalgesia in IBS (Swarbrick et al., 1980; Rossel et al., 1999). However, many studies have subsequently confirmed that IBS also involves CS and therefore enhanced sensitivity to both visceral and somatic stimuli (Verne et al., 2001; Verne and Price, 2002). Hence, generalised cutaneous heat hyperalgesia has consistently been demonstrated in IBS (e.g. (Bouin et al., 2001; Jarrett et al., 2014; Moshiree et al., 2007; Piche et al., 2010; Rodrigues et al., 2005; Vase et al., 2003; Verne et al., 2001, 2003b; Wong et al., 2010)) with the strongest degree of hyperalgesia in which the visceral afferents are likely to converge onto common spinal segments. This generalised thermal hyperalgesia has been confirmed by neuroimaging (Verne and Price, 2002; Chang et al., 2003; Verne et al., 2003a; Naliboff and Mayer, 2006). General hypersensitivity has also been found to cold pain stimulation (Bouin et al., 2001).

Earlier studies showed increases or no differences in somatic detection and pain thresholds in IBS as compared with healthy controls, but this is likely

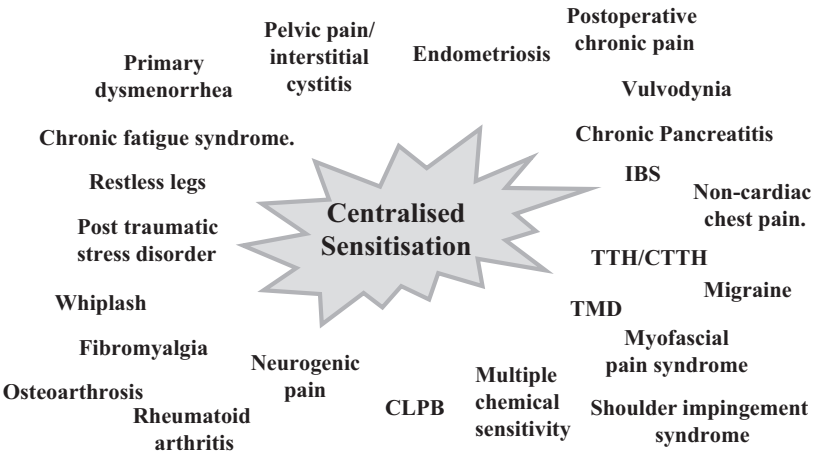

Figure 2 A listing of the many chronic pain conditions in which different aspects of the central sensitisation phenomenon have been assessed and validated mechanistically with quantitative sensory testing. (OA = Osteoarthritis, CLBP = Chronic Low Back Pain, TMD = Temporomandibular Disorders, TTH/CTTH = Tension Type Headache/Chronic Tension Type Headache, IBS = Irritable Bowel Syndrome).

explained by different methodologies rather than a change in disease characteristics (Cook et al., 1987; Accarino et al., 1995; Zighelboim et al., 1995; Chang et al., 2000).

A specific feature of visceral pain is the viscero-visceral and viscero-somatic sensitisation (Giamberardino, 2003) further supporting the central involvement.

The preferred human visceral stimulation in IBS is the rectum due to the easy access to this segment of the gut that also seems to be of major importance for the disease. However, referred pain areas following rectal stimulations are difficult to measure as they are mainly localised in perineum. As IBS is an intestinal disorder Rössel et al. assessed the referred pain areas to stimulation of the sigmoid colon. This somatic segment is normally localised in the lower abdomen. They showed that the evoked brain potentials following electrical stimulation of skin inside/outside the referred pain area differed in IBS patients, but not in controls (Rössel et al., 2001). This supports that changes in the spinal (or supraspinal) convergence of activated visceral afferents to neurones also receiving somatic input is also a key feature in IBS, again demonstration the importance of widespread changes.

5.4.2 Temporal summation

Temporal summation can be assessed in the gut by repeated electrical (Drewes et al., 1999) or mechanical stimulations (Munakata et al., 1997).

If repeated electrical stimuli are applied to the gut, the pain will increase during the stimulation and the referred pain areas expand (Arendt-Nielsen et al., 1997a). Referred visceral pain is a central phenomenon (Arendt-Nielsen et al., 2000) supporting the concept that the repeated input activates central mechanisms.

IBS patients show facilitated temporal summation to electrical colonic stimulation, and this also supports that CS plays a major role in the symptom manifestations (Rossel et al., 1999).

5.4.3 Descending pain inhibition

A number of studies have been performed on descending control in IBS patients with visceral pain. Endogenous inhibitory mechanisms are found attenuated in patients with irritable bowel syndrome (King et al., 2009; Heymen et al., 2010; Piche et al., 2011; Jarrett et al., 2014).

The less efficient CPM effect has been further validated in neuroimaging studies (Wilder-Smith et al., 2004; Song et al., 2006) and by recording of the nociceptive withdrawal reflex (Coffin et al., 2004).

Taken together, there is firm evidence that CS is present in patients with IBS.

6. Common sensitisation features across chronic pain conditions

From the above selected examples of neuropathic, musculoskeletal, joint, and visceral chronic pain it is evident that CS is present to a greater or lesser extent across the different chronic pain conditions. As the experimental methodologies used for assessing the different components differ, it is not possible to rank them according to most or least CS. However, there seems to be a tendency that deep somatic or visceral chronic conditions have the most

profound effect on the development of generalised sensitisation. As patients with, e.g. musculoskeletal pain, are among those who are to live the largest percentage of their life with their disability, the time aspect may play a role for the central manifestations.

The current summary highlights the development in the field. In the past, the contribution of CS in chronic pain was claimed to be based on non-mechanistic assessments whereas in more recent years mechanistic quantitative sensory profiling has provided more firm confirmations. However, it is, evident that the currently available tools for profiling CS are far from complete as many additional non-assessable mechanisms contribute to the manifestations.

An important finding is that for many conditions the CS can almost momentarily be reversed if the peripheral pain generators are found and inhibited or if specific receptors involved in the central pain amplification are blocked by, e.g. NMDA-antagonists. This has also been verified in preclinical studies.

Chronic pain conditions associated with psychological and psychiatric disorders can also show signs of CS which may rely less on the peripheral drive for initiation and maintenance (Arendt-Nielsen et al., 2012b).

However, the selected conditions seem representative for the central manifestations in most other chronic pain conditions (Yunus, 2007; Bourke et al., 2015) as listed in Fig. 2. Over the last decades many terms have been introduced to describe this group of pain syndromes: idiopathic pain syndromes and central sensitivity syndromes. However, as indicated above most of this name giving was uniquely based on anatomical descriptions of the painful area without any mechanistic clues.

The current state of knowledge has two immediate consequences:

(1) What is the role of CS in the development of chronic postoperative pain?
(2) How should the management strategies be optimised according to the profile of CS?

7. The role of central sensitisation for the development of chronic postoperative pain

For a long time, it has been debated how to minimise the development of chronic postoperative pain and many different approaches have been implemented (minimal surgery, nerve sparing surgery, pre-emptive analgesia, etc.). Patients with and without pain prior to surgery (e.g. thoracotomies, mastectomies) can develop chronic postoperative pain indicating that pain is not a prerequisite for this development. It is known that the pre-operative pain intensity and young age are two predictors for development of chronic postoperative pain (Pierides et al., 2016).

Factors such as physical health, mental health, preoperative pain in the surgical field, and preoperative pain are all additional contribution factors (Montes et al., 2015).

Preoperative assessment of CS using mechanistic quantitative sensory testing for predicting chronic post-operative outcome has been implemented in many laboratories in recent years (Yarnitsky et al., 2008; Granot, 2009; Wilder-Smith, 2011).

It seems that sensory tests which are considered as static methods (such as a threshold to a phasic stimulus) and not designed to assess CS are less likely to predict chronic postoperative outcome after, e.g. cholecystectomy (Bisgaard et al., 2005).

Facilitated temporal summation seems indicative of development of chronic postoperative pain after abdominal surgery (Weissman-Fogel et al., 2009) and knee (Petersen et al., 2015a) and hip (Izumi et al., 2017) alloplastic surgery. Assessing widespread hyperalgesia by pressure pain thresholds seems indicative of chronic postoperative pain outcome after knee (Petersen et al., 2016) and hip (Wylde et al., 2015) replacements.

Impaired descending pain control (Yarnitsky et al., 2008; Granot, 2009; Wilder-Smith, 2011) may to some degree be indicative of how vulnerable patients are to develop chronic postoperative pain.

Recently, combinations of the summation and CPM parameters were suggested (Carvalho et al., 2016) as even more indicative of outcome (Arendt-Nielsen, 2017). The temporal summation is generally found to be highly reliable (Staahl et al., 2006; Pryseley et al., 2009); whereas the CPM paradigm is less robust with much higher variability (Imai et al., 2016; Kennedy et al., 2016).

Both mechanisms are modulated by centrally acting drugs shown efficacy in neuropathic pain (e.g. gabapentinoids, duloxetine, venlafaxine, ketamine, buprenorphine) indicating such mechanisms are important drug targets (Arendt-Nielsen, 2015). Further studies are needed to investigate if matching patients' phenotype profiles (e.g. facilitated temporal summation + impaired CPM, facilitated temporal summation + normal CPM, normal temporal summation + impaired CPM) with drug profiles can provide valuable information guiding the development of preoperative individualised pharmacotherapy.

However, as data are still conflicting, more studies investigating prediction of sensitivity and specificity are needed.

This concept that the degree of CS seems important for the chronic outcome is further substantiated by the fact that patients with additional painful comorbidities have a higher risk of developing chronic postoperative pain after total knee replacement (Wylde et al., 2012a).

CPM normalises after pain-free recovery after joint replacement (Kosek and Ordeberg, 2000; Graven-Nielsen et al., 2012) and the widespread hyperalgesia will also be normalised (Aranda-Villalobos et al., 2013).

For some types of surgery, the patients may be offered an additional surgical procedure if they develop chronic postoperative pain. However, this may be critical as the pain system may already be in a facilitated stage. Most patients undergoing revision surgery after total knee replacement will continue to experience pain even at a higher level (Petersen et al., 2015b). Those patients with pain after revision surgery have continued enhanced temporal summation as compared with patients without pain (Skou et al., 2013) and develop more prominent spreading sensitisation than before the revision surgery (Skou et al., 2014a).

Therefore, it could be anticipated that drugs like ketamine given preoperatively could have a beneficial effect on the development of postoperative pain. However, this could not be documented with a 24 h ketamine infusion prior to thoracotomy (Duale et al., 2009) or immediately postoperatively (Joseph et al., 2012). On the contrary, some studies showed preventive effect on gabapentinoids (Sen et al., 2009; Buvanendran et al., 2010). These studies needs replication as another recent study found no effect on chronic postoperative outcome of 600 mg of gabapentin given 1 h prior to carpal tunnel syndrome surgery (Sadatsune et al., 2016), and thus there is a need for more long-term follow up studies (Zakkar et al., 2013). Furthermore, the preventive effect is not supported by pre-clinical studies (Yang et al., 2014).

8. How to interact with the central sensitisation in chronic pain?

Ideally, the prevention and management of chronic pain in patients with heightened CS should target the individually involved mechanisms. Individualised, tailored, mechanism-based therapy is currently not possible. Patient management is more complex than just addressing a few factors, but involves trial and error.

Fundamentally, two different methods of damping the CS are known: (1) blocking the peripheral drive which is maintaining the sensitisation or (2) interacting with the central transmitter systems involved in the facilitated gain.

As a peripheral block may generally have short-lasting effects and may be technically challenging to administer on a regular basis, the following will primarily focus on the interaction with central transmitter systems.

8.1 Targeting temporal summation

Over the years, many studies have shown that wind-up in rat dorsal horn neurons is inhibited by NMDA receptor antagonists (Davies and Lodge, 1987; Dickenson and Sullivan, 1987) as well as by an antagonist of the glycine site in the NMDA receptor channel complex (Chapman and Dickenson, 1992). The NMDA receptor plays a key role in temporal summation, but is very difficult to block even when using general anaesthesia or epidural analgesia. A spinal block is needed to inhibit temporal summation (Curatolo et al., 1997) whereas an epidural blockade (Curatolo et al., 1995) or volatile anaesthetics are not efficient (Petersen-Felix et al., 1996).

Examples of drugs showing an inhibitory effect on temporal summation are e.g. dextromethorphan (Price et al., 1994), ketamine (Arendt-Nielsen et al., 1995), imipramine (Enggaard et al., 2001), gabapentin (Arendt-Nielsen et al., 2007), oxycodone (Suzan et al., 2013), and venlafaxine (Yucel et al., 2005).

In a comparative study, gabapentin and carbamazepine were found to reduce temporal summation pain whereas amitriptyline increased temporal summation pain (Harding et al., 2005). This is the first study where facilitation of temporal summation has been found.

In a study by Curatolo et al. (2000), the effect of remifentanil was found to be more efficient on muscle temporal summation as compared to with cutaneous summation.

The facilitated temporal summation in chronic pain patients is efficiently inhibited by NMDA receptor antagonists (ketamine and amantadine). This has been found in patients with surgical incisions (Stubhaug et al., 1997), postherpetic neuralgia (Eide et al., 1994), phantom limb pain (Nikolajsen et al., 1996), chronic postsurgical neuropathic pain (Pud et al., 1998), and fibromyalgia (Graven-Nielsen et al., 2000).

Unfortunately, abnormal temporal summation in patients with neuropathic pain cannot predict the clinical effect of imipramine or gabapentin (Rasmussen et al., 2004) and some clinical studies have not shown an effect on facilitated temporal summation by lamotrigine (Finnerup et al., 2002) or memantine (Eisenberg et al., 1998; Nikolajsen et al., 2000).

In the studies in which the intervention reduced the temporal summation a parallel effect was seen on the clinical pain intensity indicating the importance of the central integration in CS.

8.2 Targeting descending pathways

Many preclinical studies have demonstrated drug modulatory effects on the inhibitory descending modulation including opioids, and monoaminergic agonists (e.g. Bannister et al., 2015; Ossipov, 2012; Wen et al., 2010).

From preclinical studies, it has been concluded that noradrenaline primarily promotes descending pain inhibition while serotonin promotes both descending pain inhibition and descending pain facilitation and thus may have both anti-nociceptive and pro-nociceptive effects (Suzuki et al., 2004). Serotonin-noradrenaline reuptake inhibitors (SNRIs), such as duloxetine, have a broad efficacy across a number of different chronic pain conditions, such as OA, fibromyalgia and peripheral neuropathic pain (Lunn et al., 2014).

The α2-δ ligands centrally inhibit the release of neurotransmitters (e.g. noradrenaline, serotonin, substance P) and potentially reduce CS by decreasing descending pain facilitation (Donovan-Rodriguez et al., 2006; Bee and Dickenson, 2008; Asante and Dickenson, 2010). Animal studies have validated that pregabalin reduces the descending serotonergic facilitation (Rahman et al., 2009), but as initially discussed human CPM studies cannot separate between increased inhibition and decreased facilitation. Pregabalin was also found to increase the deficient CPM in chronic pancreatitis more than placebo (Bouwense et al., 2012).

Due to the dual action of tapentadol (μ-opioid receptor agonist plus a norepinephrine reuptake inhibitor) it would be expected to enhance CPM although this was only the case for repeated administration over weeks (Niesters et al., 2014) as opposed to a single dose (Martini et al., 2015). The single dose study was conducted in healthy volunteers and it could be that an effect would have been seen in a chronic pain patient with deficient CPM.

The effect of repeated dosing with tapentadol matches very well many chronic pain conditions (Riemsma et al., 2011) with impaired CPM such as OA pain (Steigerwald et al., 2012b), LBP (Buynak et al., 2010; Steigerwald et al., 2012a; Baron et al., 2016), painful peripheral diabetic neuropathy (Schwartz et al., 2015; Vadivelu et al., 2015), and cancer pain (Kress et al., 2014).

Few studies have systematically evaluated the effects of pure opioids on CPM in healthy volunteers; oxycodone showed no effect (Suzan et al., 2013) whereas buprenorphine (Arendt-Nielsen et al., 2012a), morphine (Le Bars et al., 1992; Martini et al., 2015) and fentanyl (Arendt-Nielsen et al., 2012a) affected CPM.

There are conflicting data on the effect of naloxone/naltrexone on CPM as some found inhibition of CMP (Pertovaara et al., 1982; Willer et al., 1990; King et al., 2013a) whereas others found no effect (Peters et al., 1992; Edwards et al., 2004; Sprenger et al., 2011).

Modulatory effects on CPM have been found by dexmedetomidine (a selective α(2)-adrenoceptor agonist) (Baba et al., 2012) and apomorphine (a non-specific dopamine agonist) (Treister et al., 2013). Recently it has been suggested that calcitonin may interact with the descending pain modulation as calcitonin interacts with serotonin, and a synergetic analgesic effect between calcitonin and serotonin reuptake inhibitor antidepressants has been shown (Arendt-Nielsen et al., 2009) indicating various alternative options to interact with the descending pathways.

The evidence on the effect of ketamine on CPM is still conflicting (Niesters et al., 2013), but it may enhance pain facilitation and thereby reduce CPM (Niesters et al., 2011).

9. Limitations and future perspectives

The current review addresses mainly the pharmacological management approaches and does not address how other procedures such as exercise and the plethora of non-pharmacological strategies around cognitive modulation can influence the pain sensitisation in the selected clinical populations. The selected four clinical conditions are not entirely representative of all chronic pain stages but were selected as many quantitative, mechanistic studies have been published on CS in these groups. Furthermore, brain imaging, electrophysiological and biochemical studies were not reviewed.

Despite the indirect measures of pain sensitisation by mechanism, related proxies have been developed

and applied across different chronic pain conditions, and the results point in the same direction that chronic pain patients, despite the origin of the pain, develop different degrees of sensitisation. As the manifestations are different, it is important to develop test batteries specifically for profiling the sensitisation features in specific pain conditions. There is a particular lack of tools to profile CS in musculoskeletal and visceral chronic pain conditions. The field of linking pain phenotype with treatment (pharmacological, non-pharmacological, surgical) outcome in the context of pain has so far been slightly disappointing. Hence, there is a need to further develop tools and improve the specificity and sensitivity of the predictors.

As sensitisation is a neuroplastic phenomenon, it can change rapidly or slowly depending on the condition. However, based on cross-sectional studies the concept is that for many conditions the sensitisation is developing slowly, but solid longitudinal studies are needed to understand the progression of sensitisation and the factors controlling this.

The educational aspects of sensitisation should be broadened up to include not only pain specialists but also other relevant clinical disciplines (e.g. surgery, oncology, gerontology, paediatric, psychiatry). This is important as chronic pain patients often cannot understand why a limited trauma or even lack of a known/visible trauma can result in such disabling pain. Explaining that the pain system is not static but dynamic and undergoes changes helps the patients to better understand and accept their current situation.

10. Conclusions

Central sensitisation appears to play a key role across many chronic pain conditions and contributes to the (1) transition process from acute to chronic pain, (2) amplification of pain in existing chronic pain conditions, and (3) promotion of the development of chronic post-operative pain.

Features such as spreading sensitisation, enhanced central temporal integration, and disproportional balance between descending inhibitory and facilitatory pathways will promote pain when acting individually or together. In addition to the many other factors (e.g. genetics, psychological, psychiatric, social) involved in chronic pain, it is important to consider quantitative tools for mechanistic phenotyping of patients as this may provide information helping to select the most appropriate mono- or polypharmacy and hence develop more individualised targeted pain management regimes.

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