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Review

Central sensitization: Implications for the diagnosis and treatment of pain

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ABSTRACT

Nociceptor inputs can trigger a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways, the phenomenon of central sensitization. Central sensitization manifests as pain hypersensitivity, particularly dynamic tactile allodynia, secondary punctate or pressure hyperalgesia, aftersensations, and enhanced temporal summation. It can be readily and rapidly elicited in human volunteers by diverse experimental noxious conditioning stimuli to skin, muscles or viscera, and in addition to producing pain hypersensitivity, results in secondary changes in brain activity that can be detected by electrophysiological or imaging techniques. Studies in clinical cohorts reveal changes in pain sensitivity that have been interpreted as revealing an important contribution of central sensitization to the pain phenotype in patients with fibromyalgia, osteoarthritis, musculoskeletal disorders with generalized pain hypersensitivity, headache, temporomandibular joint disorders, dental pain, neuropathic pain, visceral pain hypersensitivity disorders and post-surgical pain. The comorbidity of those pain hypersensitivity syndromes that present in the absence of inflammation or a neural lesion, their similar pattern of clinical presentation and response to centrally acting analgesics, may reflect a commonality of central sensitization to their pathophysiology. An important question that still needs to be determined is whether there are individuals with a higher inherited propensity for developing central sensitization than others, and if so, whether this conveys an increased risk in both developing conditions with pain hypersensitivity, and their chronification. Diagnostic criteria to establish the presence of central sensitization in patients will greatly assist the phenotyping of patients for choosing treatments that produce analgesia by normalizing hyperexcitable central neural activity. We have certainly come a long way since the first discovery of activity-dependent synaptic plasticity in the spinal cord and the revelation that it occurs and produces pain hypersensitivity in patients. Nevertheless, discovering the genetic and environmental contributors to and objective biomarkers of central sensitization will be highly beneficial, as will additional treatment options to prevent or reduce this prevalent and promiscuous form of pain plasticity.

1. Introduction

In 1983 I published a study indicating that many features of the pain hypersensitivity accompanying peripheral tissue injury or inflammation were the direct result of an augmentation of sensory signaling in the central nervous system [255]. A central amplification during angina pectoris had been postulated exactly 100 years before by W. Allen Sturge MD, who in an 1883 paper in Brain envisaged a possible central nervous system "commotion ..... passed up from below" that somehow contributed to the clinical features of ischemic cardiac pain. However, the importance of this clinical insight lay largely dormant for a century, except for one human volunteer study on secondary hyperalgesia that was recognized by the authors as suggestive of a possible central contribution to the spread of pain sensitivity [101]. What I found in a pre-clinical study on stimulus–response relations in the spinal cord was that the afferent activity induced by peripheral injury triggered a long-lasting increase in the excitability of spinal cord neurons, profoundly changing the gain of the somatosensory system [255]. This central facilitation manifested as a reduction in threshold (allodynia), an increase in responsiveness and prolonged aftereffects to noxious stimuli (hyperalgesia), and a receptive field expansion that enabled input from non-injured tissue to produce pain (secondary hyperalgesia) [51,255–256,268,273].

I have recently reviewed the circumstances surrounding the discovery of the activity-dependent synaptic plasticity in the spinal cord that generates post-injury pain hypersensitivity [259], and that became termed "central sensitization" [272], as well as the current state of understanding of the cellular and molecular mechanisms responsible for this form of neuronal plasticity [147]. What I would like to specifically address in this review are the clinical implications of the phenomenon. What has central sensitization taught us about the nature and mechanisms of pain in patients,

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and what are the implications of central sensitization for pain diagnosis and therapy? Before doing this though, it is important first to understand exactly what central sensitization represents, how it has changed our general understanding of pain mechanisms, as well as reviewing the substantial data on central sensitization derived from studies on experimental pain in human volunteers.

2. What is central sensitization?

Prior to the discovery of central sensitization, the prevailing view on pain processing in the central nervous system was of a largely passive neural relay that conveyed by encoded action potentials, information on the onset, duration, intensity, location and quality of peripheral noxious stimuli, much like a telephone wire, from one site to another. More specifically, the CNS pathway was seen to constitute particular anatomical connections in the spinal cord, brain stem, thalamus and cortex (the "pain pathway"), linking the sensory inflow generated in high threshold primary afferents with those parts of the cortex that leads to the conscious awareness of painful sensations. The spinal gate control theory by Melzack and Wall in 1965 had highlighted that this sensory relay system could be modulated in the spinal cord by inhibitory controls [163], and considerable progress had been made by the early 1980's in identifying such inhibitory circuits [18]. Indeed this, together with the discovery of enkephalins and endorphins [98,109], diffuse noxious inhibitory controls [150], transcutaneous nerve stimulation [224], and the rediscovery of acupuncture [25], generated a much greater emphasis at that time on endogenous inhibitory controls than on those factors that might increase excitation, and thereby produce pain hypersensitivity. However, there was one exception, which was related to the discovery of peripheral sensitization in the 1970's [178]. Work by Iggo [28,112] and Perl [20,33,177] had identified specific high threshold sensory neurons tuned to respond only to noxious stimuli, hence their name nociceptors [265], a term first coined by Sherrington based on his studies on noxious stimulus evoked flexion reflexes. Furthermore, first Perl and then others showed that nociceptor peripheral terminals could become "sensitized" after injury, reducing their threshold, mainly to heat stimuli, and only within the site of injury where the terminal was exposed to inflammatory modulators, the zone of primary hyperalgesia [23,41,138,146,178]. While this phenomenon is clearly a very important contributor to inflammatory pain hypersensitivity [22], it cannot account for dynamic tactile allodynia, the temporal summation of pain, or secondary hyperalgesia. Some other explanation was needed as the neurobiological basis for these symptoms, which turned out to be increased synaptic function triggered within the CNS by nociceptive inputs [257,237,268].

The realization that synapses were subject to a form of use-dependent plasticity that could increase their strength or efficacy had steadily gained ground by the early 1980's. The phenomenon had first been described in the CNS as short lasting a post-tetanic potentiation of mono synaptic IA synaptic input to motor neurons by Lloyd in 1949 [155], one that could spread to other synapses on motor neurons [21]. This was followed by the discovery of windup in dorsal horn neurons by Mendell and Wall in 1965 [164], where repeated low frequency stimulation of a nerve at constant C-fiber strength was found to elicit a progressive increase in action potential firing over the course of the stimulus. A transformative breakthrough was the first description of long term potentiation (LTP) in the hippocampus by Bliss and Lomo in 1973, where a brief high frequency coincident input produced a persistent increase in synaptic efficacy, opening the door for an extensive and still ongoing study into the molecular mechanisms of synaptic plasticity. LTP was first recorded in the spinal cord in 1993 [182], where it represents a particular component of the general phenomenon of central sensitization [113,114,122]. In 1976 Kandel and colleagues described a sensitization of the gill withdrawal reflex in the sea snail Aplysia, which was associated with a facilitation of the synapse between sensory and motor neurons [29]. However, these data were interpreted as reflecting memory and learning rather than an invertebrate model of pain hypersensitivity, although of course the two phenomena converge in this, and in other model systems, although there are differences too [122,274].

What I found in my original study by 1983 and subsequent preclinical studies with colleagues at University College London was that a brief (~10–20 s), low frequency (1–10 Hz) burst of action potentials into the CNS generated by electrical stimulation or natural activation of nociceptors increased synaptic efficacy in nociceptive neurons in the dorsal horn of the spinal cord and this lasted for tens of minutes after the end of the conditioning stimulus [50,51,230,244,245,255,256,263,264,267,272,273]. This phenomenon differed from windup, which represented a progressively increasing output during the course of a train of identical stimuli (technically called homosynaptic potentiation); central sensitization was concerned instead with the facilitation that manifested after the end of the conditioning stimuli, and that once triggered remained autonomous for some time, or only required a very low level of nociceptor input to sustain it. Furthermore, central sensitization represented a condition where input in one set of nociceptor sensory fibers (the conditioning input) amplified subsequent responses to other non-stimulated non-nociceptor or nociceptor fibers (the test input; this form of facilitation is termed heterosynaptic potentiation to distinguish it from homosynaptic potentiation where the test and conditioning input are the same) [231]. The classic form of LTP in the hippocampus is homosynaptic with changes in efficacy restricted to activated synapses, a convergent plasticity, and while this is a feature of some aspects of central sensitization [190], most of its clinically relevant attributes relate to its divergent heterosynaptic components [147]. The underlying neurobiological basis for central sensitization is that for most central circuits, the receptive field properties of neurons defined by the firing of action potentials is only the "tip of the iceberg". Most of the synaptic input to neurons is subthreshold [262,263], acting subliminally either because synaptic input is too weak or membrane excitability is restrained by inhibitory inputs. Increasing synaptic strength by a presynaptic increase in an excitatory transmitter release or in the post synaptic response to the transmitter [46,100,129,130,133,151,152,154,227,231,247,264,271] or by reducing inhibition [12,103,168,180,165,208,226] or increasing membrane excitability can recruit these normal subthreshold inputs to suprathreshold action potentials, producing profound changes in functional properties [270]. More recently it has become appreciated that in addition to activity-dependent synaptic plasticity, changes in microglia, astrocytes, gap junctions, membrane excitability and gene transcription all can contribute to the maintenance of central sensitization [43,44,47,48,88,104,186,189,205,234]. Figs. 1 and 2 summarize sensory processing under normal circumstances and the changes that result from induction of central sensitization.

An important implication of these early basic science studies was the possibility that the pain we experience might not necessarily reflect the presence of a peripheral noxious stimulus. We learn from our everyday experience interfacing with the external environment to interpret pain as reflecting the presence of a peripheral damaging stimulus, and indeed this is critical to its protective function. Central sensitization introduces another dimension, one where the CNS can change, distort or amplify pain, increasing its degree, duration, and spatial extent in a manner that no longer directly reflects the specific qualities of peripheral noxious stimuli, but rather the particular functional states of circuits in the CNS. With the discovery of central sensitization, pain

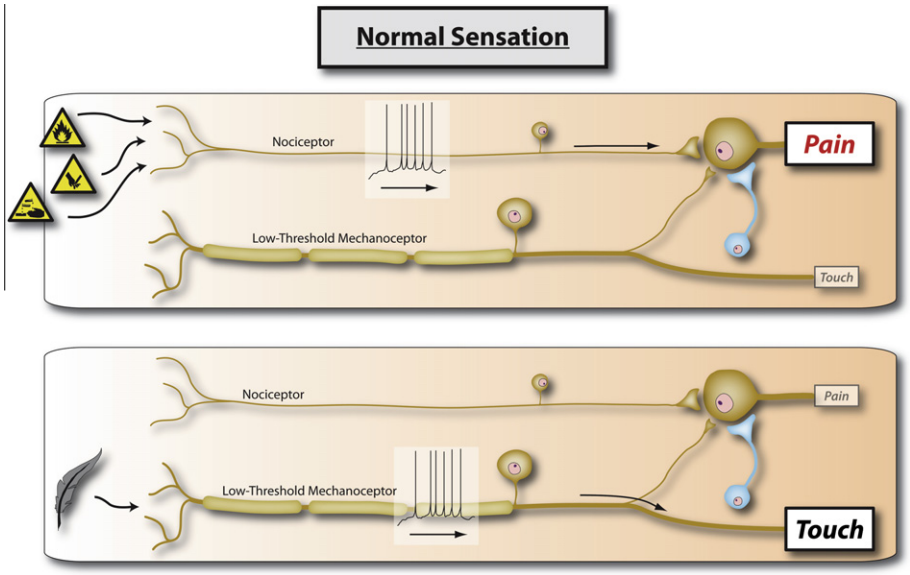

Fig. 1. Normal sensation. The somatosensory system is organized such that the highly specialized primary sensory neurons that encode low intensity stimuli only activate those central pathways that lead to innocuous sensations, while high intensity stimuli that activate nociceptors only activate the central pathways that lead to pain and the two parallel pathways do not functionally intersect. This is mediated by the strong synaptic inputs between the particular sensory inputs and pathways and inhibitory neurons that focus activity to these dedicated circuits.

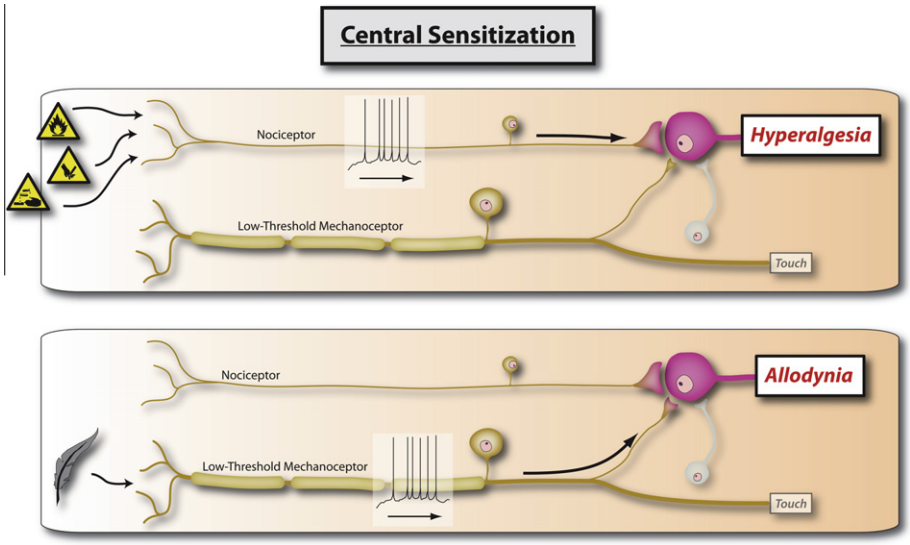

Fig. 2. Central sensitization. With the induction of central sensitization in somatosensory pathways with increases in synaptic efficacy and reductions in inhibition, a central amplification occurs enhancing the pain response to noxious stimuli in amplitude, duration and spatial extent, while the strengthening of normally ineffective synapses recruits subliminal inputs such that inputs in low threshold sensory inputs can now activate the pain circuit. The two parallel sensory pathways converge.

conceptually at least had become "centralized" instead of being exclusively peripherally driven. In this sense central sensitization represents an uncoupling of the clear stimulus response relationship that defines nociceptive pain. Nociceptive pain reflects the perception of noxious stimuli. In the absence of such potentially damaging stimuli there is no nociceptive pain. However, after the discovery of central sensitization it became clear that a noxious stimulus while sufficient was not necessary to produce pain. If the gain of neurons in the "pain pathway" in the CNS was increased, they could now begin to be activated by low threshold, innocuous inputs. In consequence pain could in these circumstances become the equivalent of an illusory perception, a sensation that has the exact quality of that evoked by a real noxious stimulus but which occurs in the absence of such an injurious stimulus. This does not mean that the pain is not real, just that it is not activated by noxious stimuli. Such pain can no longer be termed nociceptive, but rather reflects a state of induced pain hypersensitivity, with almost precisely the same "symptom" profile to that found in many clinical conditions. This raised the immediate obvious question, was central sensitization a contributor to clinical pain hypersensitivity?

These notions were generally not very well received initially, particularly by physicians who believed that pain in the absence of pathology was simply due to individuals seeking work or insurance-related compensation, opioid drug seekers, and patients with psychiatric disturbances; i.e. malingerers, liars and hysterics. That a central amplification of pain might be a "real" neurobiological phenomenon, one that contributes to diverse clinical pain conditions, seemed to them to be unlikely, and most clinicians preferred to use loose diagnostic labels like psychosomatic or somatoform disorder to define pain conditions they did not understand. We can now 30 years later, based on data from many studies in human

volunteers and patients, address whether central sensitization, defined operationally as *an amplification of neural signaling within the CNS that elicits pain hypersensitivity*, is a real phenomenon or not, and can assess its relative contribution to inflammatory, neuropathic and dysfunctional pain disorders in patients [53,258].

3. Central sensitization in human volunteers

The first clear demonstration of central sensitization in human volunteers came from a psychophysical study by LaMotte and colleagues on the secondary cutaneous hyperalgesia that is elicited by intradermal capsaicin injection (which activates the TRPV1 receptor). They found intense localized pain lasting minutes at the injection site, followed immediately by three zones of hyperalgesia; a small zone of heat hyperalgesia close to the injection site lasting 1–2 h, an intermediate zone of dynamic tactile allodynia spreading beyond the area of heat hyperalgesia and lasting several hours, and the largest zone to pinprick, way outside of the injection site, which remained present for up to 24 h [145]. The investigators then showed that the secondary mechanical hyperalgesia required sensory inflow to the CNS because local anesthesia prior to the capsaicin injection blocked it. In addition because the pain sensitivity crossed a tight band that prevented circulation in the skin, they concluded that it was not due to a local spread of the capsaicin or any peripheral inflammatory mediator. An even more direct demonstration that activity-dependent central sensitization was responsible for tactile allodynia and secondary hyperalgesia in humans came from a second study by La Motte, this time with Torebjork in 1992 [233]. They again used intradermal injection of capsaicin to induce an area of tactile allodynia that lasted for 2 h. Nerve block experiments revealed that while the capsaicin and heat pain was carried by C fibers, the mechanical allodynia was transferred to the CNS by low threshold myelinated fibers. The most elegant part of the study was their finding that electrical intraneural stimulation of single Aβ mechanoreceptive fibers that elicited a non-painful tactile sensation before the capsaicin injection, began to produce pain if the fibers' receptive field fell within the zone of secondary mechanical hyperalgesia. Lidocaine anesthesia of the cutaneous innervation territory of the stimulated fiber did not reverse the pain, showing that this was not peripheral in origin. They concluded that the pain evoked by stroking the skin area surrounding a painful intradermal injection of capsaicin "is due to reversible changes in the central processing of mechanoreceptive input from myelinated fibres which normally evoke non-painful tactile sensations".

Another early study, this time by Koltzenburg and Torebjork, using mustard oil (which activates TRPA1) as the pain conditioning stimulus, together again with differential nerve blocks, confirmed that brush-evoked mechanical allodynia was mediated by low threshold Aβ fibers that normally encode non-painful tactile sensations [140]. Unlike after capsaicin, however, the mustard oil evoked tactile allodynia required an ongoing low level input from C-nociceptors to sustain it, indicating that different sensory fibers may have different central actions, some short and others long lasting, and indeed further studies have shown differences in the duration of tactile allodynia after capsaicin and mustard oil [139], the significance of which was not appreciated a the time because it was not clear then that these irritants acted on quite different TRP receptors.

That central sensitization could cause a spread of pain sensitivity across peripheral nerve territories, the neurological dogma for diagnosing a disease of the central rather than peripheral nervous system was shown by Max and colleagues using the intradermal capsaicin model in volunteers together with radial or ulnar nerve blocks to clearly identify individual nerve territory [192]. Complementing this, a study comparing skin hyperaemia induced by a skin burn injury found that the skin blood flow changes induced by the injury had disappeared by the time secondary mechanical hyperalgesia peaked, and the two were not correlated in time or space, supporting the conclusion that peripheral mechanisms do not contribute to secondary hyperalgesia [198]. Perhaps even more dramatic, was the relatively recent demonstration that intradermal capsaicin induces contralateral hyperalgesia and allodynia that are delayed in their manifestation and reduced in extent compared to the ipsilateral secondary hyperalgesia, but present in a majority of subjects [206], a form perhaps of "tertiary hyperalgesia" that cannot be peripheral in origin. What pain sensitivity we feel then, can be determined by the state of excitability of neurons in the CNS.

Central amplification of Aδ nociceptor fiber test input following a C-fiber conditioning input was shown to contribute to pinprick/punctate secondary hyperalgesia, again using the intradermal capsaicin model [279], underscoring the different identity of the afferent signals that elicit central sensitization as a conditioning stimulus (C-fibers) from those that elicit allodynia (Aβ) or hyperalgesia (Aδ), a further clear manifestation of heterosynaptic facilitation. In a similar vein, another study found that pin prick hyperalgesia induced in response to intradermal capsaicin was actually mediated by capsaicin-insensitive afferents, showing that the test and conditioning inputs in this setting are quite different [87], while the secondary hyperalgesia elicited by intradermal capsaicin was shown by yet other investigators, to be restricted to mechanical stimuli, with no correlation between the magnitude of capsaicin evoked pain and the extent of punctate or tactile secondary hyperalgesia [237]. Furthermore, temporal summation to pin prick in the zone of capsaicin injection (as model of homosynaptic facilitation/windup) was mechanistically independent of the development of secondary hyperalgesia, because while the gain of the stimulus–response relationship in the zone of secondary was increased that of the windup was not changed, even though the actual pain was enhanced [158]. A similar conclusion was made after a study where repeated intradermal capsaicin injections were reported to produce a progressively diminishing pain, presumably due to desensitization, while the allodynia and punctate hyperalgesia continued to increase [254]. Two more recent studies using high frequency stimulation as the conditioning input to mimic conditions that elicit LTP found that while changes in the conditioned site (homotopic site) do occur, they are accompanied by a development of pain hypersensitivity in the adjacent non-stimulated heterotopic site (reduction in threshold, pain evoked by light tactile stimuli, and exaggerated response to suprathreshold pinprick stimuli [136,240], and both sets of investigators concluded that heterosynaptic facilitation predominates in this model of central sensitization, exactly as it does for the low frequency conditioning inputs that mimic the natural firing range of nociceptors. Generalizing, it seems clear that heterosynaptic changes are a major feature of the presentation of central sensitization.

Apart from changes in subjective pain measures, the consequences of central sensitization can also be detected using objective biomarkers. These include long-term changes in nociceptive withdrawal reflexes [24] and increases in cortical event related potential amplitudes [240]. Magnetic source imaging reveals an increase in the excitability of neurons in the somatosensory cortex evoked by low threshold Aβ stimulation within the capsaicin-induced zone of secondary hyperalgesia [17], while magnetoencephalography detects changes in the patterns of cerebral processing [159] and functional MRI, and changes in BOLD signals in the cortex, both during secondary hyperalgesia [16]. Another MRI study found changes in the brainstem that are apparently specific to central sensitization, in addition to the changes in the primary somatosensory cortex that are related to the intensity of pain [153].

While most studies have looked at the effects of skin conditioning stimuli on skin pain sensitivity, experimental muscle pain produced by hypertonic saline injections produces long lasting

changes in thermal sensitivity in the area of referred pain [203], while sustained nociceptive stimulation of myofascial trigger points induces a wide spread central sensitization [273,275]. Interestingly, in pre-clinical models, muscle and joint conditioning afferents have a longer lasting action in producing central sensitization than those from skin [244]. A reverse approach has shown that cutaneous capsaicin increases myofascial trigger point pressure sensitivity in segmentally related muscles [211]. Conditioning nociceptive stimuli originating in viscera, such as exposure of the lower esophagus to acid, also induces central sensitization, leading to viscerovisceral (pain hypersensitivity in the upper esophagus) and viscerosomatic hypersensitivity (allodynia on the chest wall) [193] that can be captured by esophageal evoked potentials [194], and is associated with increased temporal summation [196]. A recent study has replicated this esophageal model of central sensitization using acid and capsaicin infusions, showing also thermal and mechanical pain hypersensitivity in the rectum after the esophageal stimulation [27], indicating how widespread the effects of central sensitization are in the gastro-intestinal tract. These changes may be mechanistically related to widespread clinical pain syndromes [95].

One emerging area of considerable interest is the utility of experimental central sensitization in human volunteers to test efficacy in centrally acting drugs. Drugs with efficacy in pre-clinical models, such as NMDA receptor antagonists [271] can be tested in Phase 1b human proof of principle studies [212]. Ketamine inhibits central temporal summation [8] and secondary mechanical hyperalgesia [142] evoked by repetitive nociceptive electrical stimulation in humans as well as primary and secondary hyperalgesia after an experimental burn injury [116], visceral conditioning inputs [251,253] and topical [6] or intradermal [204] capsaicin, but not A delta mediated nociceptive pain [181]. Ketamine's action on experimental pain can be detected by fMRI [210]. Similar activity is found for i.v. dextromethophan [115]. Collectively these data strongly support a role for the NMDA receptor in acute activity-dependent central sensitization [147]. However, the trials also indicate the lack of therapeutic index between reducing central sensitization and inducing psychotomimetic side effects. Another class of drugs that has been extensively studied in human experimental models of central sensitization is the gabapentanoids. Oral gabapentin at doses similar to that used for chronic neuropathic pain when given to human volunteers reduced tactile allodynia and decreased mechanical secondary hyperalgesia elicited by intradermal capsaicin [92]. Even single administration of gabapentin had an antihyperalgesic effect on capsaicin-induced secondary hyperalgesia and reduced fMRI signatures of central sensitization [110]. In another study gabapentin, interestingly reduced cutaneous evoked central sensitization but not muscle pain [201]. Two studies have looked at pregabalin's efficacy in experimental human central sensitization, one evoked by electrical stimuli [49] and the other by intradermal capsaicin [246]. Both of these double blind studies demonstrated efficacy for pregabalin in terms of experimental tactile allodynia and secondary hyperalgesia. These data suggest that a major component of gabapentin or pregabalin's mechanism of action is a reduction of central sensitization [238]. Many other centrally acting drugs with analgesic efficacy in patients reduce central sensitization preclinically, including duloxetine, milnacipran and lamotrigene [15,118,170] but have not been tested for this action in humans. Drugs that have failed to show efficacy in human studies of activity-dependent central sensitization are NK1 receptor antagonists [252] [49] and COX-2 inhibitors [35,49,250]. A COX-2 inhibitor does have efficacy though if the central sensitization is triggered by peripheral inflammation [225], as predicted by pre-clinical models [189].

Interestingly, while gender has been described as important for differences in nociceptive pain sensitivity, a study on the secondary hyperalgesia induced by heat and capsaicin did not reveal a gender difference [119]. Nevertheless, recent data show that pain sensitivity including secondary hyperalgesia and brush evoked allodynia is heritable, with an estimated 50% genetic contribution to the pain variance [172]. The genetic polymorphisms involved in the differential susceptibility to secondary hyperalgesia have not been comprehensively investigated, although some candidates are beginning to be identified in studies of experimental central sensitization [228]. This is an area that requires major research.

The following conclusions can be made from this survey of the published studies of experimental pain hypersensitivity in human volunteers. Central sensitization is a robust phenomenon, readily induced in human volunteers in response to diverse ways of activating nociceptors (electrical stimulation, capsaicin, mustard oil, acid, heat burn, UV burn, hypertonic saline). Generally this activity-dependent plasticity manifests immediately, but its effects persist for many hours beyond the inducing conditioning stimulus, eventually returning, however, back to baseline, indicating its usual full reversibility. The phenomenon can be elicited by conditioning skin, muscle or visceral organs, and typically presents as dynamic tactile allodynia and punctate hyperalgesia but also enhanced pressure, and in some cases, thermal sensitivity, spreading from the conditioning site to neighboring non-stimulated sites, and even to very remote regions. Although there is a homosynaptic (homotopic) aspect to the phenomenon, its major manifestation is heterosynaptic (heterotopic), and for this reason and its reversibility, it is perhaps inaccurate to equate central sensitization with the LTP like phenomena in the cortex that are specifically associated with long term memory. Because central sensitization can be induced in almost all subjects and detected using subjective and objective outcome measures and is sensitive to pharmacological interventions, it is a useful tool for determining the activity of drugs on centrally driven pain hypersensitivity.

Globally, the data obtained in human volunteer studies demonstrate that induction of use-dependent central facilitation in nociceptive central pathways increases pain sensitivity and may, therefore, contribute to clinical pain syndromes. Experimental studies in human volunteers are necessarily restricted to use non-injurious conditioning inputs, and therefore are limited to studying only the activity-dependent components of pain hypersensitivity elicited by sensory inputs, and not those transcription-dependent and structural changes that manifest after inflammation or nerve injury, which may have different mechanisms, time courses and presentations [53,97,121,123,160,171,189,229,242,261,269]. The limited experience with more severe human experimental injury indicates that central sensitization also contributes to the late hyperalgesia present in this model [58,176].

4. Central sensitization and the clinical pain phenotype

What features of the clinical phenotype may be contributed to, or generated exclusively by central sensitization? While the human experimental studies reviewed above indicate that if a patient has dynamic tactile allodynia, secondary punctuate/pressure hyperalgesia, temporal summation and sensory aftereffects, central sensitization may well be involved. Any sensory experience greater in amplitude, duration and spatial extent than that would be expected from a defined peripheral input under normal circumstances qualifies as potentially reflecting a central amplification due to increased excitation or reduced inhibition. These changes could include a reduction in threshold, exaggerated response to a noxious stimulus, pain after the end of a stimulus, and a spread of sensitivity to normal tissue. However, because we cannot directly measure sensory inflow, and because peripheral changes can contribute to sensory amplification, as with peripheral sensitization, pain hypersensitivity by itself is not enough to make an

irrefutable diagnosis of central sensitization. A further complication is that because peripheral input commonly is the trigger of central sensitization, a reduction in pain sensitivity produced by targeting a peripheral trigger with a local anesthetic does not exclude central amplification, but may rather indicate a role of peripheral input in maintaining it [140]. Nevertheless, there are some features of patient's symptoms which are more likely to indicate central rather than peripheral contribution to pain hypersensitivity. These include pain mediated by low threshold Aβ fibers (determined by nerve block or electrical stimulation), a spread of pain sensitivity to areas with no demonstrable pathology, aftersensations, enhances temporal summation, and the maintenance of pain by low frequency stimuli that normally do not evoke any ongoing pain. To assess how central sensitization may present in patients, we need a detailed phenotyping of different patient cohorts to capture exactly what changes in sensitivity occur, where and when [9,11,55,86,93,188,197]. Ideally this should be combined with objective measures of central activity, such as fMRI, so that clear diagnostic criteria for determining the presence of central sensitization in patients can be established. The utility of diagnostic criteria for the presence of central sensitization would not only be insight into the pathophysiological mechanisms responsible for producing pain but more so in defining potential treatment strategies. If a particular patient's pain is primarily the result of abnormal activity in nociceptors, as in patients with primary erythromelalgia [74], the optimal therapy required is likely to be different from a patient whose tactile allodynia and secondary hyperalgesia are entirely maintained by central sensitization due to changes in synaptic efficacy in the spinal cord. This is the rationale for a mechanism-based approach to the diagnosis and treatment of pain [258,266]. Indeed response to a trial treatment, such as to the NMDA receptor antagonist ketamine, can itself be a potential diagnostic for the presence central sensitization.

5. To which clinical syndromes does central sensitization contribute?

Given the caveats about the lack of absolute diagnostic criteria for identifying the presence of central sensitization in patients, a fairly large number of studies have nevertheless putatively identified this phenomenon as contributing to patients' pain phenotype. I will briefly review these, based on disease.

5.1. Rheumatoid arthritis (RA)

Patients with RA, the prototypic inflammatory joint disease, have extra-articular tenderness which is correlated with the extent of joint disease [141] but whether this is the result of peripheral or central sensitization has not been studied. A study on juvenile chronic arthritis reported enhanced sensitivity to noxious stimuli both at joints and in remote areas in patients with and without active disease, suggesting the possibility that the disease when active sets up a state of autonomous central sensitization [107].

5.2. Osteoarthritis (OA)

This degenerative joint disease with characteristic destruction of cartilage and alteration in bone is a very common cause of chronic pain, particularly in the elderly. The degree of pain does not always correlate with the extent of joint damage or presence of active inflammation raising the possibility that there may be a central component to the pain [26]. Supporting this is the enhanced degree and duration of pain and secondary hyperalgesia evoked by intramuscular injection of hypertonic saline in patients with OA compared to controls [13]. Patients with high pre-operative pain and a low pain threshold have a higher risk of persistent pain after total knee replacement for OA, which was interpreted as reflecting central sensitization [157]. Another study on 62 patients showed that pain of central neural origin (widespread reduced pressure pain thresholds) negatively impacted on knee functional capacity [117]. OA patients have a lower pain threshold and have punctate hyperalgesia in areas of referred pain, which is associated with greater activation in the brainstem as detected by fMRI, representing a possible biomarker for central changes [99]. The centrally acting amine uptake inhibitor duloxetine which reduces central sensitization in pre-clinical models [15,124] significantly reduced pain more than placebo in an RCT in 231 patients with knee OA pain [45], indicating that drugs that target central sensitization are efficacious in this patient population. In a recent phenotyping study in 48 patients with painful knee OA and 24 age matched controls, the patients had reduced pressure pain thresholds both at the joint and in remote areas, and increased temporal summation. While the degree of sensitization correlated with the pain, it did not correlate with radiological findings, leading to the conclusion that central sensitization is an important contributor to knee OA pain [7]. Collectively, these data intriguingly suggest that the pain of OA, a peripheral pathology, has an important central component, and this is clearly deserving more study to understand its extent, mechanism and therapeutic implications.

5.3. Temporomandibular disorders (TMD)

Unlike OA, the pathophysiology of this syndrome is much less well understood. However, TMD has been found to be associated with an increase in generalized pain sensitivity after isometric contraction of the orofacial muscles [166], and widespread bilateral mechanical [78] and thermal [175] pain sensitivity are reported in women with myofascial TMD compared to age matched controls, which was interpreted as suggesting widespread central sensitization. In addition, a greater referred pain is elicited from the more frequent trigger points that are found in these patients, than in controls [77].

As for other types of facial pain, mechanical allodynia is a major feature of periradicular inflammation (periradicular periodontitis) with reduced threshold also in contralateral non inflamed teeth, reflecting central sensitization [132]. After a third molar extraction evidence for central sensitization could be detected for at least a week (enhanced response to repetitive intraoral pinprick and electrical stimulation, aftersensations and extraoral hyperalgesia) [126].

5.4. Fibromyalgia (FM)

One of the first suggestions that fibromyalgia patients may have generalized central sensitization came from a psychophysical study that identified widespread reduction in thermal and mechanical pain thresholds, as well as greater cerebral laser evoked potentials [90], a finding replicated soon after [156]. Another early small study using ketamine, showed an NMDA-dependent component to fibromyalgia and suggested that tender points may represent secondary hyperalgesia due to central sensitization [209]. Supporting this, Arendt-Nielson and colleagues found in small study that fibromyalgia patients had lower pressure thresholds and increased temporal summation to muscle stimulation, and that intramuscular hypertonic saline injections provoked a longer lasting and more widespread pain. In a related study, they found that the referred pain, temporal summation, muscular hyperalgesia and muscle pain in fibromyalgia patients were all attenuated by ketamine [96]. In 2001, Staud and Price begun a series of studies on fibromyalgia, first showing temporal summation and after sensations of the pain elicited by repetitive cutaneous thermal stimuli and repetitive mechanical stimuli to muscles

[221]. In a second study they found that temporal summation occurred at substantially lower forces and at a lower frequency of stimulation in fibromyalgia patients than in control subjects, and that painful after sensations were greater in amplitude and more prolonged [215]. The enhanced experimental pain in fibromyalgia patients was shown to contribute to the variance of the clinical pain [220]. These investigators then showed that the maintenance of experimentally induced pain in fibromyalgia patients requires significantly less frequent stimulation than in normal controls, and concluded that this heightened sensitivity to very low frequency inputs contributes to the persistent pain in these patients [218]. A later study showed that the temporal summation of pain and its maintenance was widespread, and could be equally elicited from hands or feet, leading to the conclusion that central sensitization in these patients was generalized across the neuraxis [219]. In an fMRI study they then found a stimulus and frequency dependent activation in several brain regions in fibromyalgia patients and controls, including ipsilateral and contralateral thalamus, medial thalamus, S1, bilateral S2, mid- and posterior insula, rostral and mid-anterior cingulate cortex. The stimulus temperatures necessary to evoke equivalent levels of brain activity were, however, significantly less in fibromyalgia patients, suggesting that the enhanced neural mechanisms in fibromyalgia are not the result of selective enhancement at cortical levels [216]. The Staud and Price group then designed experiments to see if peripheral sensitization may contribute to the enhanced temporal summation of thermal pain in fibromyalgia patients and concluded that it does not, based on thermal thresholds [214]. Recently they have found using local anesthetic injections though, that peripheral input from muscle appears to be important in maintaining central sensitization in FM patients [217]. This would mean that fibromyalgia may have both peripheral and central contributions, whose extent may vary from patient to patient. Certainly muscle afferents seem to have a potent capacity in pre-clinical [244] and experimental human studies [275] to induce central sensitization.

A quantitative sensory testing study in 85 fibromyalgia patients and 40 matched controls found that the patients had altered heat and cold thresholds and a reduced tolerance for pain, as well as a reduced nociceptive reflex threshold, a measure of central excitability [65]. The latter finding was sufficiently different from controls that the authors suggest it could be used as a diagnostic measure of central sensitization, identifying patients for whom centrally acting drugs may be particularly beneficial. Other studies have confirmed the increased generalized sensitivity in FM patients to pressure and thermal stimuli [94,173,179] and to electrical stimulation of skin and muscle, with enhanced cortical evoked potentials [66]. The data overall seem to support a major role for central sensitization in the generation of the symptoms of FM, and the success of centrally acting treatments, such as pregabalin or duloxetine in treating these conditions, may reflect a reduction in central sensitization in these patients.

5.5. Miscellaneous musculoskeletal disorders

Chronic neck pain resulting from whiplash is associated with lowered pain thresholds in uninjured tissue [57,222]. Injection of local anesthetic into myofascial trigger points in these patients results in an immediate increase in range of motion and elevation in pressure pain thresholds, which was felt to reflect dynamic maintenance of central sensitization by afferent triggers [85]. Patients with shoulder impingement syndrome also show widespread muscle sensitivity and an increased number of trigger points [105]. A widespread (bilateral) mechanical pain hypersensitivity is observed in patients with unilateral epicondylalgia (tennis elbow) interpreted as indicating central sensitization, possibly induced by a peripheral trigger [75]. Similar generalized deep tissue hyperalgesia can also be demonstrated in patients with chronic radiating low back pain with intervertebral disc herniation [173]. Collectively these data indicate that diverse musculoskeletal disorders are characterized by a spread of pain sensitivity to deep uninjured tissue and that low level peripheral inputs may maintain this.

5.6. Headache

The first intimation that headaches have an important component mediated by central sensitization came from a study of spontaneous tension-type headaches which found that even in the absence of headache pericranial muscle tenderness was increased in patients compared to control subjects. During headache, muscle tenderness increased and thermal pain threshold decreased in the temporal region, but remained normal in the hand which was interpreted as an indication that segmental central sensitization contributed to pain in frequent sufferers of tension-type headache [120]. This was then followed by the observation by Bernstein and colleagues that cutaneous allodynia developed in 79% of patients during migraine attacks in, and sometimes beyond the area of referred pain [36,37]. This finding has been repeated in several studies since then [52,161,135,207]. While cephalic and extracephalic allodynia are well described, spontaneous body pain and allodynia have also been reported as preceding migraine attacks [56]. Laser evoked cutaneous pain thresholds are reduced during migraine attacks and cortical evoked potentials increased [62]. No change in heat pain thresholds are found in chronic tension-type headache, but there is pericranial tenderness [63,80] and hyperalgesia of neck shoulder muscles [81]. Nociceptive input from muscles has been suggested to contribute to the induction of central sensitization in tension-type headache [79], much as has been suggested for FM. In patients with cluster headaches the nociceptive flexion reflex threshold is reduced on the symptomatic side [191]. In a population study on primary headaches in 523 patients, evidence for pain hypersensitivity was found in those with tension type pain, with a greater disturbance in individuals with chronic or more frequent headaches, implying that central sensitization may contribute to the chronification of headache [30], something that is supported by epidemiological data [31]. In a longitudinal prospective study on whether increased pain sensitivity is a cause or an effect, a study in 100 individuals found that subjects had normal thresholds prior to the development of headache, but this decreased in those who then developed chronic tension-type headache, suggesting that the pain hypersensitivity is a consequence of frequent tension-type headaches, and not a predictor or risk factor [32], a finding interpreted as a showing that central sensitization plays a role in the chronification of tension-type headaches. Interestingly, a study in patients with either chronic migraine and chronic tension-type headache found in both cohorts reduced threshold for pressure, pinprick, blink, and the nociceptive flexion reflex, as well as higher windup ratios [83], possibly reflecting a common role for central sensitization in the chronification of different types of headache.

5.7. Neuropathic pain

The first demonstration of a likely contribution of central sensitization to neuropathic pain came from a study by Campbell and colleagues, who showed that an ischemic conduction block of large myelinated fibers specifically reduced dynamic tactile allodynia [42], a finding that was soon replicated [140]. Since then careful phenotyping studies of conditions like carpal tunnel syndrome have revealed enhanced bilateral sensitivity and an extraterritorial spread of symptoms in patients with unilateral or single nerve entrapment, supporting a contribution of central sensitization [61,76,82,278]. Furthermore, ketamine reduces established periph-

eral neuropathic pain [125] and chronic phantom limb pain [73] indicating that ongoing activity- and NMDA receptor-dependent synaptic plasticity may contribute to maintain neuropathic pain. That tricyclic antidepressants, dual uptake inhibitors and calcium channel alpha(2)-delta ligands, all centrally acting drugs that normalize enhanced neural activity, are the current first line treatments for neuropathic pain [72], reinforces the importance of the central component of the pain and its suitability as a target for treatment.

5.8. Complex regional pain syndrome (CRPS)

A prominent feature of chronic CRPS1 is tactile hyperesthesia and pressure hyperalgesia [241], which can be registered as enhanced S1 activation by a neuromagnetometer [243]. There is also thermal hyperalgesia in acute CRPS1 patients, which on the side ipsilateral to the diseased limb, may have a peripheral component due to ongoing aseptic inflammation, but the presence of contralateral hypersensitivity in the absence of any inflammatory changes points to an involvement of the CNS [108]. In a small randomized placebo controlled trial intravenous ketamine reduced CRPS pain [200].

5.9. Post-surgical pain

This is a very heterogenous group comprising acute postoperative pain and persistent pain of multiple causes, including surgically induced neuropathic pain [1,131]. In the acute phase, incisional pain is associated with a secondary punctate hyperalgesia that is ketamine sensitive [223], with no spread in thermal sensitivity [143] indicating induction of central sensitization. Considerable controversy exists over whether pre-emptive treatment targeting central sensitization is superior to postoperative treatment in treating either the acute postoperative pain or its transition to chronic pain [4,5,54,60,68,70,71,128,149,102,236,260]. Surprisingly, because of numerous technical problems related to the design, conduct and interpretation of such studies, this turns out to be a difficult issue to resolve [134,167]. This is not the place to review the full literature on pre-emptive analgesia, however my personal take on the available data is that there appears to be a small signal for pre- vs. postoperative analgesic treatment in some settings, but it is likely not generally clinically relevant. It seems clearly important though that patients have full analgesia established on recovery from a general anesthetic or adequate regional anesthesia during surgery, and this can be maintained until surgical healing is well advanced [19,14,277]. The treatment plan for controlling postoperative pain can potentially include drugs with action on central sensitization such as ketamine [184], pregabalin [34,162], gabapentin [202] and duloxetine [106], which in the limited number of trials currently available show some efficacy, but more RCT are required to assess their utility in treating acute postoperative pain or in reducing the risk of developing chronic pain [59].

5.10. Visceral pain hypersensitivity syndromes

Pain hypersensitivity is a feature of several common disorders of the gastro-intestinal tract including irritable bowel syndrome, non-cardiac chest pain and chronic pancreatitis that all appear to have a central sensitization component. A majority of IBS patients have both rectal and somatic hypersensitivity [249]. Repetitive sigmoid stimulation in patients with IBS induces rectal hyperalgesia and viscerosomatic referral [169]. Local rectal anesthesia reduces rectal and somatic pain in irritable bowel syndrome patients, supporting the possibility that visceral hyperalgesia and secondary cutaneous hyperalgesia in irritable bowel syndrome are the results of central sensitization dynamically maintained by input from the GIT. Patients with non-cardiac chest pain have esophageal hypersensitivity [195], with a reduced tolerance to repeated distension, increased size of referred pain and a greater propensity to show secondary hyperalgesia after acid infusion in their lower esophagus [69], all interpreted as reflecting the consequence of central sensitization. Chronic pancreatitis is associated with generalized deep pressure hyperalgesia [39,174] and patients display greater degree and spatial extent secondary hyperalgesia elicited by repetitive experimental stimulation, suggesting enhanced central sensitization [67] that is reduced by a thorascopic splanchnic denervation [38], which may reflect that visceral input from the pancreas maintains the central sensitization.

In the urological tract, pain hypersensitivity is a feature of interstitial cystitis, chronic prostatitis, endometriosis, and vulvodynia, conditions whose pathophysiology and etiology are however, poorly understood. Although central sensitization has been hypothesized to contribute [137], not much data are available and few studies have been performed. Men with chronic prostatitis have though heightened pain sensitivity in the perineum [239,276], while women with vulvodynia have an enhanced post capsaicin allodynia and secondary hyperalgesia compared to controls [84].

5.11. Co-morbidity of pain conditions characterized by pain hypersensitivity

Pain can be defined as nociceptive when it is generated by noxious stimuli, inflammatory when produced by tissue injury and/or immune cell activation, and neuropathic, when it is due to a lesion of the nervous system. What about pain conditions though, where there is no noxious stimulus, inflammation or damage to the nervous system? There are several common syndromes that present with pain hypersensitivity but no clear etiological factor, i.e. considered ‘‘unexplained” and which might actually reflect not only peripheral pathology but also a primary dysfunction of the nervous system. These include fibromyalgia, tension-type headache, temporomandibular joint disease and irritable bowel syndrome, all of which may have a specific contribution to their phenotype by central sensitization, as detailed above. If a heightened sensitivity of the CNS or an increased propensity to develop central sensitization is a common feature of these syndromes, one would expect that there may be increased co-occurrence or comorbidity of the different conditions. It is also possible that an enhanced capacity to produce or maintain central sensitization is the primary defect in some of these syndromes.

In a study on almost 4000 twins for comorbidity of chronic fatigue, low back pain, irritable bowel syndrome, chronic tension-type headache, temporomandibular joint disease, major depression, panic attacks and post-traumatic stress disorder, associations were found that far exceeded those expected by chance, and the conclusion was that these conditions share a common etiology [199]. Another large epidemiological study on 44,000 individuals including twins for comorbidity with chronic widespread pain found co-occurrence with chronic fatigue, joint pain, depressive symptoms, and irritable bowel syndrome, leading to the conclusion that associations between chronic widespread pain and its comorbidities may include genetic factors [127]. Yet another study on 2299 subjects for four unexplained syndromes; chronic wide spread pain, chronic orofacial pain, irritable bowel and chronic fatigue again found that the occurrence of multiple syndromes was greater than expected by chance [2]. These epidemiological findings strongly suggest that there may be a common mechanistic basis for these diverse conditions, and that may have a hereditary component.

Smaller studies have found comorbidity between fibromyalgia and the following conditions: migraine in females but not males [111], primary headache [64], chronic fatigue symptom [89],

systemic lupus erythematosus [213], irritable bowel syndrome [144], rheumatoid arthritis [183], the premenstrual syndrome [3], chronic urticaria [235] and cervical myofascial pain syndrome [40]. Comorbidity has been shown also for back pain and temporomandibular disorders [248], migraine and temporomandibular disorders [91], irritable bowel syndrome and functional dyspepsia, fibromyalgia and chronic pelvic pain [185], and finally between migraine and irritable bowel syndrome, chronic fatigue and fibromyalgia [232]. There is also an overlap between urological disorders like chronic pelvic pain, interstitial cystitis, painful bladder syndrome, chronic prostatitis and vulvodynia with fibromyalgia, chronic fatigue, temporomandibular disorders and irritable bowel syndrome [187], and more specifically between vulvodynia, fibromyalgia and irritable bowel syndrome [10].

The overwhelming conclusion from these diverse epidemiological studies is that chronic pain hypersensitivity in the absence of inflammation or nerve damage results in apparently phenotypically different syndromes depending on the tissue/organs affected. However, the overall similarity of the sensitivity changes may reflect a common contribution of central sensitization, and this may account for the unexpectedly high comorbid rate of the apparently different syndromes. To test if there are indeed central sensitization syndromes, we will need a clear set of diagnostic criteria and biomarkers for the phenomenon. If this hypothesis is correct, the implications may be that treatment strategies targeted at normalizing hyperexcitability in the CNS may have a shared efficacy for the different manifestations of the central sensitization syndrome.

6. Conclusions

Clinical pain is not simply the consequence of a ‘‘switching on” of the ‘‘pain system” in the periphery by a particular pathology, but instead reflects to a substantial extent, the state of excitability of central nociceptive circuits. The induction of activity-dependent increases in synaptic function in these circuits triggered and maintained by dynamic nociceptor inputs, shifts the sensitivity of the pain system such that normally innocuous inputs can activate it and the perceptual responses to noxious inputs are exaggerated, prolonged and spread widely. These sensory changes represent the manifestation of central sensitization, and extensive experimental medicine and clinical investigations over the past twenty years have revealed it to be an important component of the pain hypersensitivity present many patients. While considerable progress has been made in teasing out the cellular and molecular mechanism responsible [148], much remains still to be learned, particularly which genetic and environmental contributors increase the risk of developing central sensitization in particular systems, exactly what triggers and sustains the phenomenon, and what is responsible in some individuals for its persistence. Nevertheless, the identification of the contribution of central sensitization to many ‘‘unexplained” clinical pain conditions has both provided a mechanistic explanation, and offered a therapeutic target.

Conflict of interest

There is no conflict of interest.

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