OPINION ARTICLE

REVISED Central sensitization and pain hypersensitivity: Some critical considerations. [version 2; referees: 2 approved]

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Abstract

Since its discovery, central sensitization has gained enormous popularity. It is widely used to explain pain hypersensitivity in a wide range of clinical pain conditions. However, at present there is no general consensus on the definition of central sensitization. Moreover, the use of the term central sensitization in the clinical domain has been criticized. The aim of this paper is to foster the discussion on the definition of central sensitization and its use.

Keywords

Central sensitization, definition, pain, nociception, secondary hyperalgesia.

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version 1 published 21 Aug 2018		

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REVISED **Amendments from Version 1**

We have listed the "European Research Council 'starting' grant (PROBING PAIN 336130)" in the "Grant information" section of this version 2, as this was missed out in our previous version. We have also made a small correction in the first Introduction paragraph.

See referee reports

Introduction

"Many subjects, but by no means all, become conscious of soreness of skin surrounding a small area of injury"

With these words Sir Thomas Lewis starts one of the chapters in his book "Pain"[1] (p. 68). The sentence refers to what is now known as "secondary hyperalgesia", which has intrigued pain neuroscientists for almost a century. Lewis was probably the first that systematically studied this phenomenon. He hypothesized that secondary hyperalgesia was due to a peripheral mechanism ("nocifensor axon reflex"). Impulses generated by nerves at the site of injury travel antidromically via branches to their endings, where there is a release of substances that excite neighboring nerves[1].

However, by performing a series of psychophysical experiments Hardy *et al*.[2] came to another conclusion. Contrary to Lewis who suggested that secondary hyperalgesia resulted from a spreading of excitation in the skin, Hardy *et al*. hypothesized that secondary hyperalgesia resulted from a "central excitatory state"[2] (p. 139).

Similar to the idea of Lewis of a network of interconnected nerves, Hardy *et al*. hypothesized that in the spinal cord there is a pool of neurons consisting of primary and secondary neurons that make synaptic connections to a network of "internuncial" neurons. The function of these internuncial neurons would be to establish and maintain an excitatory state within the neuron pool. In the case of tissue injury, the barrage of noxious impulses originating from the site of injury enters the spinal cord where they excite the network of internuncial neurons, leading to an excitation of connected neurons[2].

> *"If now the skin is pricked in the area of secondary hyperalgesia, a burst of impulses passes into the spinal cord and when reaching the tertiary neuron it is facilitated giving rise to more intense sensation than usual"*[2] (p.135).

Woolf[3] was the first that provided evidence for such a "central excitatory state". He showed that in rats the motor reflex threshold elicited by mechanical punctate stimuli delivered adjacent to a burn injury was reduced for many hours[3]. In subsequent studies Woolf and co-workers further showed that the induction of this "central excitatory state" does not require tissue injury, but that it can also be induced after electrical stimulation of C-fiber nociceptors[4]. Based on these findings, Woolf and co-workers[5] introduced the term "central sensitization" (CS):

> *"This is the phenomenon of aberrant convergence; the generation of pain by activating sensory fibres that normally only produce innocuous sensations i.e. the large myelinated low threshold afferents. Aberrant convergence arises as a consequence of changes induced within the spinal cord by activity in unmyelinated afferent fibres – a process called central sensitization"* (p. 256).

Actually, Woolf *et al*. describe here what is now called allodynia*: "pain in response to a non-nociceptive stimulus"*[6].

Since 2008, the task force for taxonomy of the International Association for the Study of Pain (IASP)[6] proposes the following definition of CS:

> *"Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"*.

The task force for taxonomy[6] defines a nociceptive neuron as:

> *"A peripheral or central neuron of the somatosensory system that is able to encode a noxious stimulus"*.

But what is meant by *encoding*? And which neurons can be considered part of the somatosensory system and which not?

Nowadays the term CS is very popular and is associated with many more conditions than secondary hyperalgesia. The concept of CS is used by both basic scientists and clinicians; however its use in the clinical domain has been criticized[7]. The aim of this paper is to foster the discussion on the definition of CS and its use.

Is CS defined too broadly?

If a definition becomes too broad it will be used non-selectively and it will lose its value. On the other hand, if a definition becomes too specific it may miss important phenomena. The IASP proposal for the definition of CS clearly describes a *phenomenon*. However, in the literature CS is often presented as mechanism, for example, Vardeh *et al*.[8] (p. T56). More importantly, the definition does not mention a functional meaning. If the purpose of the term CS was and/or is to explain *pain hypersensitivity* then this should be included in the definition. Furthermore, the term "nociceptive neurons" may then not be specific enough. As pointed out by Sandkühler[9]:

> *"Nociceptive neurons comprise a heterogeneous cell group with putatively many different and sometimes opposing functions, including a large group of inhibitory interneurons. Thus enhanced responsiveness of some of these neurons could contribute to hyperalgesia. On the other hand, enhanced responsiveness of inhibitory nociceptive neurons may well lead to stronger feedback inhibition and analgesia, while still other neurons may not contribute to the experiences of pain but rather to altered motor or vegetative responses to a noxious stimulus"* (p. 708).

Woolf[10] proposed an alternative definition of CS which links CS directly to pain hypersensitivity:

> *"An amplification of neural signaling within the CNS that elicits pain hypersensitivity"* (p. S5).

However, establishing a causal relationship between CS and pain hypersensitivity is particularly difficult. Indeed, it is possible to measure the activity of nociceptive neurons in the CNS in animal preparations but obviously, we cannot measure pain perception. Conversely, we can measure pain perception in humans but we cannot directly measure the activity of nociceptive neurons[11].

In addition, because we cannot record directly from nociceptive neurons in humans and we have to rely on changes in pain perception or thresholds, the risk is to end up in a *circulus in probando*[12]. For example, patient X shows CS because she/he suffers from pain hypersensitivity and pain hypersensitivity is a manifestation of CS. The described evidence for the conclusion is not different from the conclusion itself.

Taken together, depending on the purpose of the term CS, it may be necessary to reconsider the IASP definition.

Is secondary hyperalgesia the only example of CS?

In a related note, the task force for taxonomy of the IASP[6] further states about the term sensitization:

> *"This is a neurophysiological term that can only be applied when both input and output of the neural system under study is known, e.g. by controlling the stimulus and measuring the neural event"*.

According to Treede[13] the phenomenon of secondary hyperalgesia induced by intradermal capsaicin injection

> "*…is currently the only example where both input and output of spinal neurons have been documented in the same model and, hence, the IASP definition of CS is fulfilled"* (p. 1200).

This would imply that, for the moment, the term CS, as provided by the IASP, may only be used for this particular condition.

When injected into the skin capsaicin activates TRPV1 expressing nociceptors and elicits a burning sensation[14]. A consequence is the development of increased pinprick sensitivity in a large part of the skin surrounding the injection site[14], a phenomenon reminiscent of secondary hyperalgesia after tissue injury. By recording the activity of nociceptive neurons in the primate spinal cord before and after capsaicin injection, Simone *et al.*[15] showed that both wide-dynamic-range (WDR) and high-threshold (HT) neurons respond more strongly to pinprick stimuli when these stimuli were delivered after the injection to the skin surrounding the injection site (output). The same group also recorded the activity of peripheral A-fiber and C-fiber nociceptors in this area (input) but their activity was unchanged[16]. Because these sensitized spinal neurons project via the spinothalamic pathway to the brain, they may contribute to the increase in pinprick perception in humans.

However, it remains puzzling why secondary hyperalgesia is characterized by an increase in the perception for mechanical pinprick stimuli, but not heat stimuli[17–19]. Should a sensitization of WDR neurons, which are polymodal, not also lead to an increase in perception for other modalities like touch or heat?

Nociceptive input (and increases thereof) does not necessarily elicits pain

An important function of nociception in normal conditions is to warn for tissue damage. Therefore it would make sense that nociceptors are activated *before* there is any tissue damage. Compatible with this idea are the observations that nociceptors in humans are activated by stimulus intensities that are *not perceived as painful*[20].

Indeed, in normal conditions (i.e. without sensitization) mechanical pinprick stimuli typically elicit a sharp pricking sensation, which is not perceived as painful in the majority of people. However, studies using microneurography have clearly demonstrated that such mechanical pinprick probes activate mechanosensitive nociceptors in the skin[21–23]. Moreover, a study comparing the perceptual pain thresholds in human volunteers with the thresholds for nociceptors in animals using the same pinprick probes, suggests that the non-painful sharp pricking sensation is mediated by mechanosensitive nociceptors[24].

Pinprick stimuli delivered after sensitization to the skin surrounding the site at which sensitization was induced clearly elicit an increase in intensity of perception but this is not always perceived as painful. Importantly, the perception elicited by tactile stimuli is not increased[25] (and unpublished observations), indicating that the increase in the pricking sensation elicited by pinprick stimuli after sensitization is mediated by mechano-sensitive nociceptors instead of low-threshold mechanoreceptors.

Likewise, we recently showed that heat perception elicited by tiny laser stimuli selectively activating C-fiber nociceptors in the skin was greater when these stimuli were delivered to the area of secondary hyperalgesia[26]. However, despite the fact that our heat stimuli selectively activated C-fiber nociceptors, the perception elicited by these stimuli was not qualified as painful neither at baseline (before inducing sensitization) nor after the induction of sensitization. Importantly, the greater heat sensitivity elicited by these stimuli is probably a perceptual correlate of CS. Indeed, Kronschläger *et al.*[27] recently showed in rats that strong peripheral nociceptive input activates glial cells (which include microglial and astrocytes) leading to the release of cytokines and chemokines which excites remote C-fiber synapses.

Taken together, both examples (increased pinprick sensitivity and greater heat sensitivity) suggest that CS does not necessarily result in pain hypersensitivity. This would plead for a mechanism-based approach of CS rather than focusing on changes in pain perception only. Indeed, according to the definitions provided by the IASP[6] one cannot label the increases in pinprick and heat perception as "hyperalgesia" because it is not an *increase in pain sensitivity*. They cannot be labeled as "allodynia" either, because the stimulus is a nociceptive one and is not always perceived as painful after sensitization.

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Current Referee Status: ✔ ✔

Version 2

Referee Report 23 October 2018

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✔ **Philipp Hüllemann**
Division of Neurological Pain Research and Therapy, Department of Neurology, University of Kiel, Kiel, Germany

Emanuel N van den Broeke provides a very interesting overview on how the term 'central sensitization' (CS) was originally characterized, how the use of the term developed in the scientific field and how extensively it may now be overused in basic and clinical research. The author lists several "historic" and recent scientific examples, which shine light on the mechanistic origin of central sensitization. It soon becomes clear that there is no actual consensus on the definition of central sensitization and that scientific evidence is sparse as well as contradictory on some occasions. Newer studies show that the intensity of thermal and mechanical stimuli increases most probably due to central sensitization processes but that this increase of intensity is not necessarily perceived as painful. Therefore, non-painful aspects of central sensitization are lacking in the current definition of CS. The further, we need to think of a more specific definition, which may guide researchers and clinicians in the use of the term.

I have two suggestions:

1. It might have been useful to add some sentences on peripheral sensitization and its possible role in driving, as well as maintaining central sensitization.
2. A short conclusion/summary including the authors thoughts would also be helpful.

Is the topic of the opinion article discussed accurately in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Are arguments sufficiently supported by evidence from the published literature?
Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?
Partly

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 18 October 2018

doi:10.5256/f1000research.17668.r38228

Geert Crombez
Department of Experimental-Clinical and Health Psychology, Ghent University, Ghent, Belgium

The paper by Emmanuel van den Broeke critically discusses definition and use of the terms central sensitisation and pain hypersensitivity. As stated by the author, the term central sensitisation has become increasingly popular, and seems to become over-used, if not mis-used. At times, it is important to reflect upon the origin of terms, and to track how meaning and use have changed over time. Evidently, we do not have to hold on the past, and definitions and use may change as science advances. The paper of van den Broeke is timely, and provides essential reading for many. It is an ideal paper for scholarly reflection and group discussion.

It nicely traced the origin in meaning, and the various changes in definition. It critically analyses interrelationships with other constructs, and potential disadvantages. Notwithstanding, it does not provide definite answers. Probably, that is not possible, but I would suggest that the authors reflect upon what should be the way forward. What do they recommend to readers and researchers.

Most importantly, seems to be a precise use of the term, and to avoid confusion in meaning. Indeed, as pointed out central sensitisation can be used to describe a phenomenon or to describe a mechanism. This is confusing and may result in circular reasoning: central sensitisation explains central sensitisation; In that respect, I have learned to make a distinction between at least three ways of using scientific terms: (1) as a result, (2) as an explanation and (3) as a procedure. Central sensitisation as a result refers to the phenomenon, most often as the result of a specific procedure. Indeed, there are some experimental procedures that induce the phenomenon. Finally, an scientific endeavour is to provide explanations, often mechanistic explanations, for the phenomenon that results from particular experimental procedures. In times of confusion and overuse, it is useful to come back and reflect upon what exactly is meant by someone.

Is the topic of the opinion article discussed accurately in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Are arguments sufficiently supported by evidence from the published literature?
Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?
Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Pain pscyhology, learning psychology, philosophy of causality and science; practice of science

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Discuss this Article

Version 1

Reader Comment 24 Aug 2018

André Mouraux, Université catholique de Louvain, Belgium

In this interesting and timely comment, Emanuel N van den Broeke argues that the term 'central sensitization' (CS) is extensively (over)used in the field of basic and clinical pain research, although there is no consensus on its definition. Furthermore, he stresses that if the term is defined too broadly, it will be used non-selectively and loose its value.

Indeed, the scientific community has struggled to agree on how this term should be defined. In my view, this is because the term itself is a combination of two words having very broad meanings.

The first word, 'central', simply refers to the central nervous system (CNS), as opposed to the peripheral nervous system. This has some importance, as it hints to the fact that, if one wants to counter CS, one must aim at the CNS compartment. However, it does not provide any clue of where in the CNS central sensitization should occur. Hence, the term does not justify a definition that would restrict it to "changes induced within the spinal cord" (Woolf et al., 1988). If one wants to refer exclusively to changes occurring within that structure of the CNS, a more restrictive term would be more appropriate.

The second word, 'sensitization', refers to a non-associative learning process in which the repeated administration of a stimulus, any stimulus, results in the progressive amplification of the organism's usual response(s) to a stimulus. Therefore, I do not find justified the statement of the taxonomy task force of the IASP (2008) that the term CS applies if and only if "both the input and output of the neural system under study is known" or, as later stated by Treede et al. (2016), when "both input and output of spinal neurons have been documented".

Quite the contrary, I would be inclined to consider that demonstrating increased neuronal activity in the CNS is not sufficient to demonstrate CS, because demonstrating sensitization requires to document an amplification of the organism's response to a stimulus, such as the perceptual output of the stimulus, autonomic responses, or the magnitude of the gill withdrawal reflex in the aplysia. In fact, sensitization does not even require neurons, as evidenced from the observation that repeated exposure to noxious stimuli can lead to a sensitization of the avoidance behavior of single-celled protozoans.

For these reasons, my proposal would be to accept the broad and phenomenological definition of CS that logically flows from combining the acknowledged definitions of its two constituent words. Obviously, with this phenomenological definition, demonstrating response amplification to repeated stimulation in a specific context or condition and demonstrating that this response amplification is due to a change in CNS

function is sufficient to demonstrate CS, but it is not sufficient to link this CS to any specific mechanism within the CNS. For example, linking CS in a given context or condition to enhanced synaptic transmission at spinal level would require evidence that the response amplification is indeed due to a change in the input-output function of spinal neurons, i.e. it would require that “both input and output of spinal neurons have been documented”.

Competing Interests: None.