Commentary

Central Sensitization: Explanation or Phenomenon?

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Abstract
Central sensitization (CS) is a popular concept that is frequently used to explain pain hypersensitivity in a large number of pain conditions. However, the concept of CS is now also increasingly used to explain nonpain symptoms. In the present commentary, we argue that CS, as defined by the International Association for the Study of Pain, refers to changes in nociceptive neurons only and therefore cannot be applied to enhanced responses to stimuli other than nociceptive and/or pain. Moreover, the evidence for CS in widespread pain (other than secondary hyperalgesia) and many other conditions is scarce to absent. As a consequence, CS is a descriptive label for the explanandum rather than an explanation and, as such, suffers the risk of being a circular explanation. Finally, cognitive and emotional factors should also be considered as potential mechanisms for the wide range of phenomena that are currently interpreted as evidence for CS.

Keywords
central sensitization, pain, functional syndromes

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“Scientific thinking necessitates clarity. . . . In turn, clarity hinges on accuracy in the use of specialized terminology” (Lilienfeld et al., 2015, p. 1). The aim of this commentary is to critically discuss the current use of the construct “central sensitization” (CS). CS as a construct derives from the pain field. However, it is increasingly being used to explain pain hypersensitivity in a wide variety of pain conditions such as osteoarthritis pain, low back pain, whiplash, temporomandibular, chronic (widespread) pain, and so forth (Arendt-Nielsen et al., 2018; Woolf, 2011). In addition, its popularity is rapidly growing to explain symptoms of an expanding range of other disorders. For example, CS has been advanced as an explanatory concept for chronic itch (Schmelz, 2016) and for functional somatic syndromes (FSSs) such as fibromyalgia, chronic fatigue, and irritable bowel syndrome (Bourke, Langford, & White, 2015; Nijs et al., 2012). CS has also been suggested as an explanation for idiopathic environmental illnesses, involving exaggerated responses to nontoxic chemicals, everyday electromagnetic radiation, infrasound stimulation from windmills, and so forth (Dantoft, Andersson, Nordin, & Skovbjerg, 2015). Furthermore, also the relationship between functional somatic disorders and elevated comorbidity such as migraine, elevated stress, burnout, anxiety, depression, inflammatory disease, poor sleep, cognitive deficits, and increased somatic symptom reports in general has been attributed to CS (Grassini & Nordin, 2017). In this view, CS is considered a common pathophysiological mechanism that serves as a link among different FSSs and between FSS and its associated comorbidities (Bourke et al., 2015). In fact, the term “central sensitivity syndromes” has been coined to describe this common aspect of a large array of syndromes (Yunus, 2007).

Although increased pain sensitivity in some conditions may well be a manifestation of CS, it is unclear how CS can explain the wide variety of nonpain symptoms...
mentioned above. To the best of our knowledge, CS as a term was introduced in 1988 by Clifford Woolf and coworkers (Woolf, Thompson, & King, 1988) and referred to the increased excitability of spinal nociceptive neurons triggered by peripheral nociceptive input. This was based on observations in animals that the motor reflex threshold to mechanical punctate stimuli delivered adjacent to a burn injury was decreased for many hours (Woolf, 1983), a phenomenon reminiscent of secondary hyperalgesia in humans (see below).

The International Association for the Study of Pain (IASP) task force for taxonomy defines CS as “increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input” (Loeser & Treede, 2008, p. 476). It is important to emphasize that the definition does not describe a perceptual consequence, such as an increase in pain perception, but only refers to an increased responsiveness of nociceptive neurons. A nociceptive neuron is defined by IASP as “a central or peripheral neuron of the somatosensory nervous system that is capable of encoding noxious stimuli.” However, it is unclear what exactly is meant by “encoding.” Also, the general term nociceptive neurons in the definition may not be sufficiently specific. Indeed, as pointed out by Sandkühler (2009), nociceptive neurons constitute 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)

Furthermore, the task force specified that sensitization refers to “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” (Loeser & Treede, 2008, p. 476). According to Treede (2016), currently the only example where both input and output of the system is known, and thus where the definition of CS is fulfilled, is secondary hyperalgesia induced by intradermal capsaicin injection. Capsaicin activates nociceptors and produces a painful burning sensation. As a consequence, a large area of the skin surrounding the injection site develops increased (pain) sensitivity for mechanical punctate stimuli, typically referred to as secondary hyperalgesia. This secondary hyperalgesia seems not to be mediated by a peripheral sensitization of nociceptors but instead results from an increased responsiveness of spinal nociceptive neurons (CS; Baumann, Simone, Shain, & LaMotte, 1991; Simone et al., 1991). At present, the exact spinal mechanism underlying secondary hyperalgesia remains unknown; however, new studies are emerging (Kronschläger et al., 2016).

We believe that the evidence for CS in conditions other than secondary hyperalgesia is scarce, if not absent, and that the use of CS to explain an expanding and widely varying set of phenomena relies on a hypothetical, almost metaphoric, use of the concept.

What then is the rationale for using CS to explain symptoms other than pain or nociception? Given the long and meandering struggle (Fink, 2009) to understand clinical phenomena such as FSS and medically unexplained symptoms within a medical framework, often “baffling physicians” (Lipowski, 1988, p. 1359), the concept of CS as a neurobiological explanation appears to be particularly attractive in this context. For example, in the case of FSS, Bourke et al. (2015) suggest that the mechanisms underlying pain hypersensitivity are also responsible for other symptoms in FSS. The assumptions of this account are that, first, there is spinal sensitization induced by peripheral nociceptive input as a result of tissue injury. This would result in increased activity in ascending pathways and a reduction of activity in descending inhibitory pathways. Second, there is a central augmentation of activity in neural networks involved in pain processing, including lateral (sensory-discriminative), medial (affective-motivational), and frontal (cognitive-evaluative) areas. Augmented activity in motivational and evaluative neural systems causes multimodal hyperresponsivity with increased salience detection regarding a large variety of stimuli, unfiltered threat detection, and a nearly permanent state of response readiness. Eventually, this would explain the co-occurrence of enhanced pain perception in FSS with comorbid psychiatric disorders, sleep disturbance, and dysregulation of autonomic and neuroendocrine systems resulting in the large array of somatic complaints that is typically found in FSS. Taken together, in FSS, CS is typically used to explain enhanced responses to emotionally relevant stimuli as measured by self-reports and with stress-related bodily parameters.

While ultimately enhanced responding in neural systems must be involved, the definition of CS, as proposed by the IASP, in itself does not explain the enhanced responsiveness of the central nervous system (CNS) to emotionally relevant stimuli other than pain or nociception. Most importantly, CS as an explanation in such conditions runs the risk of being circular: CS is defined as enhanced responding in several response systems, and the explanation for this enhanced responding is
CS. In other words, the described evidence for the conclusion is not different from the conclusion itself. In this way, CS is a label for the explanandum rather than an explanation.

Besides the problem of circularity, by restricting oneself to the construct of CS as an explanation for FSS, one excludes other relevant possible explanations. For example, a long-standing tradition within learning psychology has investigated the conditions for habituation, sensitization, (associative) learning, and generalization of emotional responses and somatic complaints. Importantly, this perspective may also elucidate increases in pain: It has been shown that hyperalgesia can be induced by classical conditioning (see Madden et al., 2016, for a review and meta-analysis). In addition, a substantial body of evidence exists on the role of cognitive and emotional factors for pain, somatic complaints, and FSSs, such as appraisal processes, negative expectations, repetitive negative thinking (e.g., worrying, catastrophizing), hypervigilance for bodily sensations, increased arousal, and fear. For example, in the context of pain, it has been shown that negative expectations can increase secondary hyperalgesia (van den Broeke, Geene, van Rijn, Wilder-Smith, & Oosterman, 2014) and that a nocebo treatment induced elevated autonomic arousal, which prevented hyperalgesia from extinguishing (Colagiuri & Quinn, 2017). There is ample evidence for the role of those factors in elevated symptom reports and stress-related responses in FSSs and in many other conditions that are currently linked to CS as an explanation (Van den Bergh, Witthoft, Petersen, & Brown, 2017). It is therefore not clear how replacing these variables by CS as an explanatory concept will move our understanding forward.

In sum, we conclude that (a) the term CS, as defined by the IASP, refers to changes in nociceptive neurons only and therefore cannot be applied to enhanced responses to stimuli other than nociceptive and/or pain; (b) the evidence for CS in widespread pain (other than secondary hyperalgesia) and many other conditions is scarce to absent; (c) at this moment, CS is a descriptive label for the explanandum rather than an explanation and, as such, suffers the risk of being a circular explanation; and (d) the explanatory role of learning and cognitive and emotional factors should be considered as potential mechanisms for the wide range of phenomena that are currently interpreted as evidence for CS. We therefore propose to reserve the term CS for the phenomenon related to its discovery: the increased excitability of spinal nociceptive neurons triggered by peripheral nociceptive input.

**Author Contributions**

E. N. van den Broeke and O. van den Broeke discussed and drafted the first version of the manuscript. All the authors approved the final version of the manuscript for submission. E. N. van den Broeke and O. van den Broeke contributed equally to this work.

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