1 Title:

2 Central sensitization in humans: popular phrase or useful concept?

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To the Editor:

The review article *“Central sensitization in chronic pain and medically unexplained symptom research: A systematic review of definitions, operationalizations and measurement instruments”* by den Boer et al. [1] published in the January issue of this journal is timely and important. It shows that central sensitization (CS) has various definitions in the literature and as a result is operationalized in many different ways.

Historically, the term *central sensitization* derives from the pain field and was introduced by Woolf and colleagues [2]. It was based on the discovery that in animals peripheral nociceptive input triggers a state of increased spinal cord excitability [3]. Currently, CS is defined by the International Association for the Study of Pain (IASP) as: *“Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input”* (www.iasp-pain.org). The IASP 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”* (www.iasp-pain.org). According to Treede [4] 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.

The aim of den Boer et al. was to enhance clarity regarding the term CS which then *“provides a solid basis for further scientific research and clinical use”*. Based on their analysis of selected papers, the authors arrived to the conclusion that *“there is consensus that hyperexcitability of the central nervous system is the central mechanism in the definition of CS”*. However, we would like to argue that this phrase is so broad that it is not quite informative. In fact, it can be interpreted as that CS includes all types of amplifications in the CNS, and thus not only nociception. Hence, we are not convinced that this conclusion *“provides a solid basis for further scientific research and clinical use”*.

It is not surprising that the authors arrive to such a broad phrase considering that if one extracts a common ground from many different definitions, the result is the “lowest common denominator”. In our opinion, the discovery that the central nervous system can amplify or generate pain has been so appealing that CS has been broadened to include any increase of an aversive somatic sensation. Indeed, it is not only considered an explanatory concept for chronic pain, for which direct experimental evidence is still lacking, but also for a large number of other symptoms that cannot be linked to peripheral physiological dysfunction (so-called medically unexplained symptoms, MUS).

We find it unlikely that the variety of phenomena seen in people with chronic pain and MUS are generated by a single process. Instead, we are convinced that these complex conditions involve multiple processes (e.g. non-associative and associative learning) and/or mechanisms. Therefore, we do not see the need to catch all these different aspects in a

single broad definition. First, because broadening the definition will increase the number of people that fits the definition, but it will also increase the heterogeneity of processes involved. Second, as a result, it will not lead to a better treatment. Moreover, to use CS as explanation for the enhanced responding in neural systems 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 [5].

To conclude, we appreciate the attempt of the authors to provide clarity regarding the definition and operationalization of central sensitization, however, we believe that *“hyperexcitability of the central nervous system”* is a too broad phrase and therefore not informative. Moreover, we question the conclusion that CS might be a valuable explanation to understand both chronic pain *and* MUS.

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