



Redefining sensitization could be a sensitive issue

Roger B. Fillingim

Commentary on: van den Broeke EN, Crombez G, Vlaeyen JWS. Reconceptualizing sensitization in pain: back to basics. PAIN Reports 2024;9:e1125.

In the pain field, sensitization is having a moment. Indeed, the concept of sensitization features prominently in framing many of the topics that currently attract much of our scientific attention, including chronic overlapping pain conditions,⁵ the transition from acute to chronic pain,^{8,11} and mechanism-based diagnosis and treatment of pain.^{1,13} Moreover, pain hypersensitivity (ie, sensitization) is a central (no pun intended) aspect of the clinical criteria for the new mechanistic pain category of nociplastic pain.⁴ Given the significance of sensitization in pain research, it might be surprising to know that there remains no consensus as to the meaning of this term. In their perspective article in this issue, van den Broeke, Crombez, and Vlaeyen¹² highlight the variability in how sensitization is defined and conceptualized in our field. As the authors note, sensitization often has been defined in terms of neural mechanisms. For example, the IASP defines sensitization as “increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normal subthreshold inputs.”³ One outcome of this definition is that sensitization cannot be assessed clinically because we do not have access to nociceptive neuronal responses in our patients. This type of definitional and conceptual confusion is not unique to sensitization. For example, the term stress has been used to describe threats to homeostasis (eg, hypoglycemia, emotional distress, and environmental exposures) as well as physiological and psychological responses to such threats (ie, the definition by Selye: “the nonspecific response of the body to any demand on it”).^{2,10} Regardless of the field, this type of confusion around the meanings of commonly used terms can impede scientific progress.

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Community Dentistry & Behavioral Science, University of Florida College of Dentistry, Gainesville, FL, USA

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Admirably, van den Broeke et al. propose a solution to this definitional confusion—returning to the original behavioral meaning of the term. Specifically, they propose that sensitization be defined as “enhanced behavioral responsiveness that results from repeated or prolonged exposure to the same stimulus.” The advantages of this definition lie in its specificity—in particular it disambiguates response from mechanism, and it lends itself to operationalization because behavioral responses can be directly measured in clinical settings. Furthermore, because the definition is mechanistically agnostic, it does not require inference about underlying neurophysiological events. I applaud the authors for raising these important issues and proposing a solution because definitional clarity is crucial for moving science forward. This is consistent with increasing efforts in the field of ontology, which fully recognizes the critical need for definitional precision when organizing information and moving research fields forward.⁷ And logically, it makes sense to clarify the definition of sensitization because a reasonable person might ask whether the same term should be applied to neural recordings obtained from a rodent, perceptual responses of human participants undergoing quantitative sensory testing, behavioral responses to an experimental stimulus, and patients completing a self-report questionnaire (eg, the Central Sensitization Inventory⁶)?

I suspect many would agree that reducing confusion surrounding the term sensitization is an important goal, in which case several issues regarding the authors’ proposed definition warrant some discussion. First, the authors’ conceptualization is firmly grounded in a behavioral perspective, which has the advantage of emphasizing observable and measurable responses. However, many experts in the field likely consider sensitization an internal state or process that certainly can affect behavior, but these conceptualizations imply that sensitization could well be ongoing even in the absence of behavioral evidence. It strikes me that this conceptualization parallels how we often think about pain itself. That is, we generally gain information about others’ pain through their verbal and nonverbal behavior, but we would not infer that in the absence of such behavior their pain is no longer present. That is, evidence of a phenomenon is not equal to that phenomenon. Furthermore, as technological advances continue to enhance the precision with which we can assess neural responses in humans, it seems suboptimal to exclude these nonbehavioral responses from our definition of sensitization. Thus, I suspect the authors’ insistence

that sensitization be defined in terms of behavioral responses will be unsatisfactory to many, especially for those who view sensitization as a potentially enduring neurobiological phenomenon.

The proposed definition of sensitization also relies heavily on “repeated or prolonged exposure to the same stimulus.” Although this facilitates the design of experiments investigating sensitization, its application to many clinical situations is less clear. Specifically, in real-world clinical settings, the link between stimulus and behavior is often tenuous. The stimulus affecting an individual’s pain-related behavioral response may be vague or completely unknown. Relatedly, enhanced behavioral responses are often observed in the absence of any clear stimulus. Perhaps these examples could be resolved by allowing that the stimulus in question could be an endogenous event (eg, a thought or neural activity); however, these types of stimuli would not be directly measurable in most human applications, which reduces the operationalizability of the phenomenon.

These concerns notwithstanding, I fully support the authors’ goal of increasing the precision with which we think and talk about sensitization. The authors’ definition accomplishes this but requires endorsing their behavioral conceptualization. Although the debate over what comprises sensitization plays out, we can apply other strategies to enhance our precision in discussing this important concept. For example, future authors who are addressing the topic should clearly articulate their definition(s) of sensitization, including a description of how sensitization was measured in their primary research or in the previously published work to which they refer. In addition, adjectival qualifiers could also be used for clarity to convey how sensitization is being conceptualized and measured (eg, behavioral sensitization or neural sensitization). Because our clinical assessments cannot provide direct information regarding neural mechanisms, if we insist on neurophysiological definitions of sensitization, we should adjust our language accordingly. Indeed, Schuttert et al.⁹ recently introduced the term Human Assumed Central Sensitization, recognizing the uncertainty surrounding inferences about underlying neurophysiological mechanisms when assessing people with chronic pain conditions.

van den Broeke et al.¹² have highlighted the imprecision and ambiguity surrounding current definitions of sensitization and proposed a solution. Although I anticipate resistance to their behavioral conceptualization of the term, I am hopeful that the ensuing discussions about this topic will produce enhanced clarity in how we think about, measure, and describe sensitization.

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