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Reconceptualizing sensitization in pain: back to basics

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1. Introduction

When a sensory stimulus is presented repeatedly or prolonged to an organism the behavioural response to that stimulus decreases (habituation), increases (sensitization), or remains unchanged. Habituation and sensitization are considered the simplest forms of (nonassociative) learning (learning is defined as *changes in the behaviour of an organism that result from regularities in the environment of the organism*.[4] In the case of nonassociative learning changes in behaviour are due to regularities in the presence of 1 stimulus[4]) and have been studied since the beginning of the previous century.[22]

It is hard to identify who introduced the terms habituation and sensitization in the literature. However, Harris in his extensive review[11] proposed to use the term habituation to describe the behavioural response decrement as a result of repeated stimulation. In the same period, the term sensitization was used in the context of pseudoconditioning[7,8,10]: *"an effect arising from repeated presentation of the unconditioned stimulus"*[10] (p. 501) and referred to the augmentation of reflexes, such as the eyelid response.[7,8,10]

At least 2 approaches can be taken in the study of habituation and sensitization. The first approach aims at identifying behavioural characteristics of the phenomenon under study ("behavioural approach"). The second approach attempts to explain the phenomenon in terms of neural mechanisms ("neural approach").

Groves and Thompson,[9] when formulating the dual-process theory, integrated both approaches. The terms habituation and sensitization were used to refer to the hypothetical neurophysiological processes in the central nervous system that interact to produce the net behavioural response to repeated stimulation, whereas the terms "response habituation" and "response sensitization" were used to describe the decrease of increase in behavioural response. However, in this way, habituation and sensitization are used for both the explanandum (behavioural response) and explanans (neurophysiological process).

In 2007, the term sensitization was introduced to the basic pain terminology of the International Association for the Study of Pain (IASP).[16] The IASP defines sensitization as the increased responsiveness of nociceptive neurons,[13] and considers it to be a neurophysiological term that *"can only be applied when both input and output of the neural system under study are known,* eg, *by controlling the stimulus and measuring the neural event*."[13] Depending on the level of the nervous system where sensitization is generated, the IASP distinguishes between peripheral and central sensitization. Hence, the IASP follows a neural approach for the study of sensitization.

Apart from the IASP definition, many other definitions and interpretations of sensitization exist in the literature,[2] thereby raising further confusion. For example, Woolf[26] (p. 4) and others[17,19] define central sensitization as *"amplification of neural signalling within the central nervous system that elicits pain hypersensitivity."* Moreover, some researchers interpret central sensitization as a generalized or global state of central nervous system sensory amplification[12] that accounts for a general increase in sensitivity explaining a variety of nonpain symptoms that can be measured with the Central Sensitization Inventory.[12,17,18] Furthermore, the term central sensitization has been used variably, eg, for denoting a mechanism,[17,19,23] a diagnosis,[17] and a disorder.[6]

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2. Sensitization: back to basics

To avoid further confusion about the term sensitization, we propose to restore the definition of the term to its original meaning: a response increment as a result of repeated stimulation. Moreover, and equivalent to the definition of habituation,[21] we propose to confine the use of the term sensitization to behaviour because this is what we ultimately wish to understand and which is applicable to both animals and humans.

To experimentally study sensitization, we propose to make a distinction between *procedure, effect,* and *mechanism*.[3] Procedure refers to the design of the experiment, stimuli used, and responses registered. Effect refers to the result of the procedure, ie, the observed outcome. Mechanism explains why the effect is observed. Hence, we propose to label sensitization as the *behavioural outcome* of a procedure and not as a mechanism.

The distinction between procedure, effect, and mechanism is applicable to different levels of analysis. We encourage being precise in distinguishing these concepts and to use whenever possible dedicated terminology specific to the level of analysis (eg, wind-up for labelling the increased responsiveness of spinal wide-dynamic-range neurons in response to repeated C-fiber stimulation).

Sensitization may also occur in response to a prolonged stimulus and may affect more behaviour parameters than response magnitude only. For that reason, we propose to operationally define sensitization as *enhanced behavioural* (there is currently no consensus on the definition of behaviour,[1,15] and for the sake of limited space, we have omitted a thorough discussion on this topic) *responsiveness that results from repeated or prolonged exposure to the same stimulus*. Enhanced responsiveness may include a higher magnitude or frequency of the behavioural response or faster reaction times and refers to the comparison with a nonhabituated baseline stimulus (eg, the first stimulus or first part of the stimulus in the case of a prolonged stimulus, **Fig. 1A**). Theoretically, stimulus repetition may also change an initial response to a more defensive response. For instance, nonpainful but intense electrical stimulation may become painful after repeating the electrical stimulus. Another example could be a prolonged heat stimulus that could be perceived (depending on intensity) initially as nonpainful but may become painful after some time. The switch to a more defensive response during the repetition (or prolongation) of the same stimulus should also be considered sensitization (enhanced responsiveness). Sensitization is different from dishabituation[21] (**Fig. 1A**).

Figure 1B, panel 1, shows the procedure to observe sensitization. In this case, response magnitude is taken as example. The response (R^A) to a certain stimulus (S^A) increases compared with baseline after repeating or prolongation of the stimulus. Thus, the test stimulus is the same as the inducing stimulus. This is the classical example of sensitization.

However, stimulus repetition or prolongation may also lead to what is called *cross-sensitization*; the enhanced behavioural responsiveness elicited by a new stimulus not involved during stimulus repetition (**Fig. 1B**, panels 2–3).[20] The first type is when repetition of stimulus S^A leads to the increase (when taking response magnitude as example) of the same response but elicited by another stimulus (S^B). The second type is when the repetition of stimulus S^A leads to the increased response elicited by another stimulus (S^B).

In addition to these types, we propose a third type of cross-sensitization (**Fig. 1B**, panel 4). In this case, the repetition of stimulus S^A triggers the same response (R^A) to stimulus S^B, whereas S^B initially elicited another response (R^B). For example, the change of a tactile sensation elicited by a tactile stimulus into a pain sensation after the repetition of another stimulus. Hence, in this type of cross-sensitization, there is no increase in response of the second stimulus (S^B) but rather a *change in the response to a more defensive response*.

Evidently, sensitization can be evaluated in intact organisms only, ie, where the peripheral and central nervous system are able to process the applied stimuli.

3. A case for a better understanding of sensitization in the context of pain

To better understand behaviour, Krakauer et al.[14] proposes that a first and necessary step is to develop a conceptual framework that attempts to answer the question *why* organisms behave in that particular way. In the context of pain the question would be why do humans sensitize to stimuli eliciting pain? Once agreement has been reached, questions such as *how* become relevant.[14] To illustrate this, Krakauer et al. gave the example of

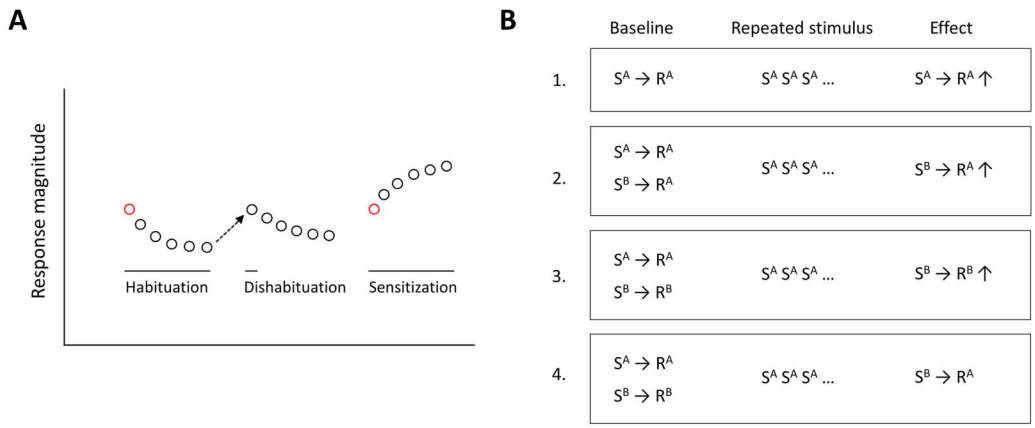

Figure 1. (A) Illustration of habituation, dishabituation, and sensitization. Each circle represents a hypothetical response to the same stimulus. For this illustration, response magnitude is taken as example. Habituation is a decrease in responsiveness with repeated stimulation (first red circle is the baseline stimulus). Dishabituation is the recovery of a habituated response (arrow) to its baseline level (red circle in the example of habituation). Sensitization is the increase in responsiveness with repeated stimulation. The first stimulus (red circle) serves as the baseline stimulus. (B) Types of sensitization. The letter S refers to the stimulus, and the letter R to the response. 1. Sensitization. 2 to 4. Cross-sensitization.

the bird flying analogy. "*Once we agree that bird flight is an adaptive behavior, we then determine that it flies by flapping it wings and not by wiggling its feet. Once we have worked this out, we can start studying the feathers that make up the wing*"[14] (p. 485). The observation that behavioral characteristics of sensitization are seen across phylogeny (some characteristics of sensitization are even seen in aneural single cells[5]) indicates that sensitization may have a behavioral advantage.[24] In those cases when the organism encounters stimuli that have the potential to harm or threaten the integrity of the body, the resulted sensitization can be considered a defensive response. The aim of this defensive response is to protect the integrity of the body and to prevent (further) tissue injury.[25]

Based on the analogy, we first need to systematically characterize which type of stimuli and parameters induce sensitization and cross-sensitization effects. The second step would be to study contextual influences. Animal studies have shown that nonassociative learning can be modulated by the animal's state and a variety of environmental factors.[27] To establish the contribution of each of the factors and others (eg, social interaction, pain history, anxiety, fear, stress etc.) to sensitization, new and carefully designed experimental behavioural studies in humans are needed. The third step would be to understand how the sensitization effects comes about, based on existing or new theories.

Disclosures

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