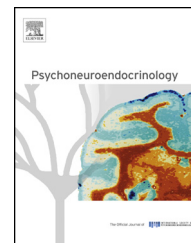




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INVITED REVIEW

# Brain sensitization to external and internal stimuli



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## KEYWORDS

Sensitization;  
Subjective health complaints;  
Unspecific illness;  
Cognitive behavior treatment;  
Comorbidity;  
Cognitive activation theory of stress

**Summary** Sensitization is defined as a non-associative learning process occurring when repeated administrations of a stimulus result in a progressive amplification of a response (Shettleworth, 2010). The purpose of this review paper is to discuss whether brain sensitization is helpful in common health problems in man. The paper reviews data on brain sensitization covering increased behavioral, physiological, cognitive, and emotional responses in man and animals. The paper concludes that brain sensitization may be a helpful concept to understand subjective and “unexplained” health complaints (nonspecific muscle pain, mood changes, fatigue, and gastrointestinal complaints), and, therefore, relevant for evidence based treatment and prevention of these common health problems.

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## 1. Introduction

Sensitization is defined as a non-associative learning process occurring when repeated administrations of a stimulus result in the progressive amplification of a response (Shettleworth, 2010). In this paper brain sensitization covers increased behavioral, physiological, cognitive, and emotional responses, and is used for data from man and animals. The main emphasis is on the behavioral phenomena that are ascribed to changes in neurons in the nervous system (Ursin and Eriksen, 2007). The main purpose is to discuss whether this term is helpful in explanation of common health problems in man (unspecific muscle pain, mood changes, fatigue, and gastrointestinal complaints), and, if so, relevant for evidence based treatment and prevention of these common health problems.

The starting point for the discussion is neurophysiological data from animals, from simple neuronal networks to experiments on mammalian brains (Squire and Kandel, 1999). The discussion is then advanced to even more complicated systems, including behavioral, cognitive, endocrine, metabolic, clinical, and epidemiological data from man and animals. Finally, the potential value of the conclusions will be tested for available evidence based on data from prevention and treatment of the health problems in man.

It is beyond the scope and resources of this paper to give a comprehensive and systematic review of the literature. The limitations in the selection are based on several biases. The term “stress” is used strictly within a systematic and comprehensive stress theory (the Cognitive Activation Theory of Stress, CATS, Ursin and Eriksen, 2004). Clinical and epidemiological data are mainly from “welfare states” in Northern Europe, in particular from the Nordic European countries. These countries have generous compensation systems for all citizens and free or almost free medical care. At least in Norway the sickness compensation is 100% of the regular salary, the compensation for permanent disability is at least 80%. Even if it is surprising to foreign observers, and against theories in economy, the majority of Norwegians still go to work every day. A small group of the working population (10%) has most of the sick leave (80%) (Tveito et al., 2002). There is virtually no unemployment in Norway.

## 2. Sensitization and habituation

When mammals are presented with a new unexpected stimulus they show an orienting response, which is remarkably similar across species. There is an initial arrest of ongoing activity, followed by a general increase in arousal and searching movements toward the source of the stimulus. If the stimulus is repeated, the response reappears for the next 10 or 15 presentations, with decreasing intensity. Then the

response disappears. This is referred to as habituation. If the stimulus is changed, or other stimuli are presented, the orienting response reappears.

If the first responses are compared for intensity, there is often an increase in response. The second and third responses are more pronounced than the first response. This is referred to as sensitization. The dual-process theory of Groves and Thompson (1970) covers the relation between habituation and sensitization. A new stimulus triggers two opposing processes. Sensitization decrease gradually as habituation finally extinguishes the response. This is particularly evident in experiments on the orienting response, however, the two processes have also been identified in data on the synaptic mechanisms, for instance from the spinal cord in mammals (Svendsen et al., 1999; Cervero, 2009).

## 3. Sensitization

On the cellular level, sensitization is an increased efficiency in a neural circuit, due to a change in the synapses from repeated use (Collingridge et al., 2004). This feed-forward mechanism increases the response to a stimulus. Arguments have been raised to use the term exclusively for the cellular process of enhanced excitability (Cervero, 2009). In this paper, as in much of the clinical and behavioral literature, sensitization is used in a broader perspective. A cognitive analog has been suggested by Brosschot and van der Doef (2006). An attentional bias gives priority to thoughts and information related to fears and somatic complaints. Patients with unspecific health complaints show sensitization and extensive activation of cognitive networks related to illness and pain. Brosschot refers to this as the “night and day watch” of the sensitized organism. There are several reports giving clinical support for this mechanism. For instance, phantom limb pain patients that “catastrophize” show stronger pain responses, they show more attention and anticipation to pain (Vase et al., 2011). Attacking this cognitive style is essential in our present cognitive treatment programs for muscle and back pain and fatigue (Sveinsdottir et al., 2012).

The purpose of this paper is to examine whether this neurobiological sensitization hypothesis fits the clinical data, in particular whether this offers a plausible explanation of whether and why these complaints appear to occur in comorbid clusters. If you have one complaint you most probably have a lot of other complaints as well.

## 4. The neurophysiology of sensitization and habituation

There is a vast literature explaining the role of habituation to non-signal stimuli. The orienting response is a safety mechanism to guarantee a response to any new stimulus. Habituation

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