

## Habituation to pain: a motivational-ethological perspective.

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## 1 Introduction

Habituation, defined as “*a behavioral response decrement that results from repeated stimulation and that does not involve sensory adaptation/sensory fatigue or motor fatigue*” (pp. 136, [40]), is ubiquitous. It is observed across species, stimuli and responses, but in pain it is studied far less than the opposite ‘sensitization’. Habituation to pain is mainly studied using external pain stimuli in healthy volunteers, often to identify the underlying brain mechanisms, or to investigate problems in habituation in specific forms of pain (e.g. migraine). Although these studies provide insight, they do not address one pertinent question: why do we habituate to pain? Pain is a warning signal that urges us to react [13]. Habituation to pain may thus be dysfunctional: it could make us unresponsive in situations where sensitivity and swift response to bodily damage is essential. Early theories of habituation were well aware of this argument. Sokolov [49] argued that responding to pain should not decrease, but rather increase with repeated exposure, a phenomenon he called ‘sensitization’ (see also [35]). His position makes intuitive sense: why would individuals respond less to pain that inherently signals bodily harm? In this topical review, we address this question from a motivational-ethological perspective.

First, we describe some core characteristics of habituation. Second, we discuss theories that explain *how* and *when* habituation occurs. Third, we introduce a motivational-ethological perspective on habituation and explain *why* habituation occurs. Finally, we discuss how a focus on habituation to pain introduces important methodological, theoretical and clinical implications, otherwise overlooked.

## 2 Characteristics of habituation?

Ten behavioral characteristics of habituation have been identified [20,40,54] (see Table 1). These occur in all organisms across stimulus modalities. The key characteristics of habituation were proposed over forty years ago [20,54], but are still current [40]. Some, such as dishabituation, are important to dissociate habituation from sensory adaptation and motor fatigue. *Dishabituation* is found when, after successful habituation to a stimulus, introduction of a different stimulus (i.e. the dishabituating stimulus) results in increased responding to the original stimulus [40]. Although habituation may often be described as short-term (minutes or hours), it can persist over days (long-term habituation). Perhaps one of the most interesting characteristics with respect to painful stimuli is that “Within a stimulus modality, the less intense the stimulus, the more rapid and/or more pronounced the behavioral response decrement. *Very intense stimuli may yield no significant observable response decrement*” (pp. 137, [40]). Sensitization may thus be expected to be the default

response to a series of painful stimuli, and habituation would only occur under specific circumstances (see e.g. [18]).

[insert Table 1 about here]

### 3 How does habituation occur?

Several models attempt to explain the processes underlying habituation (see [53] for an overview). Here we briefly discuss cognitive models [28,32,50,64], a central tenet of which is that with repeated exposure to a stimulus, organisms build a cognitive representation of its features. When this cognitive representation matches the actual stimulus, responding to that stimulus is inhibited. When a mismatch occurs, as when a repeated stimulus changes, the organism responds accordingly. Thus these models predict that repeated exposure to painful stimuli will result in habituation to those stimuli.

Other studies that focus on the underlying brain mechanisms show that habituation to pain involves various brain mechanisms (e.g. [41]). For example, Bingel et al. [3] reported that the decreased self-report of repetitive painful heat stimuli is reflected in decreased BOLD responses to nociceptive stimuli in pain processing regions including the thalamus, insula, secondary somatosensory cortex and the putamen. By contrast, pain-related BOLD responses in the subgenual anterior cingulate cortex, involved in endogenous pain control, increased over time. This suggests that habituation of responses to pain is at least in part mediated by increased central anti-nociceptive activity. Although these models describe *when* and *how* habituation to painful stimuli occurs, they largely fail to explain *why* habituation to pain occurs.

### 4 Why do we habituate to pain? A motivational-ethological perspective.

Little in the pain literature addresses the '*why*' question. We may find some examples in ethology, the study of animal behavior in its environment, where habituation to particular stimuli also makes no sense at first sight. In ethology, habituation to potential life-threatening events has been extensively studied. For example, young animals at risk of predation respond to a wide variety of stimuli [36] but, with experience, they learn to narrow the range and habituate to those that are harmless. One often cited example is the anti-predator crouching response of gallinaceous birds to flying objects. Newly hatched chicks crouch or perform other defensive behaviors to a wide variety of stimuli flying overhead. After a few uneventful experiences (e.g. flying sparrow, falling leaves, ...) their crouching response to innocuous stimuli wanes, and is only elicited by unfamiliar flying objects, such as goshawks. Learning not to crouch at the sight of every overhead stimulus has obvious selective advantage. As this example illustrates, habituation to life-threatening events should be

highly specific, as any mistake could be fatal. However, if it is too selective, animals waste energy in defensive behavior to innocuous stimuli. Habituation is also dependent on the context in which the stimulus appears. Animals habituate to some predators at a certain position in space or at a certain time, whereas they learn that predators at other locations or other times are harmless [23,38,65]. Interestingly, prey animals never *fully* habituate to nearby predators; they remain attentive to the predator's actions while tolerating its presence. Orienting is still present, but without disruption of ongoing behavior [55]. Mallard ducks, for example, continue to orient toward hawk and goose models after they have ceased to evoke any overt fear responses [30], even after more than 2000 presentations.

Although predators constitute an external threat, whereas pain poses an internal threat, parallels can be drawn between anti-predator behavior in animals and reactions to pain. Predators constitute a potential threat to survival; likewise, pain signals a potential threat to physical integrity. Both predators and pain interrupt ongoing behavior. However, if the presence of the predator or pain is unlikely to be associated with bodily damage, it is adaptive to habituate to it so that other important activities can be pursued. Habituation to biologically significant events may then best be considered as learning *not* to react to stimuli that do not have detrimental consequences, thus preventing reaction to false alarms. On the other hand, sensitivity and specificity of this decision must be delicately balanced, as failure to detect a harmful stimulus may be fatal. Next, we discuss several characteristics of habituation to pain from a motivational-ethological perspective. Many of these have not been systematically explored in pain research.

#### 4.1 Specificity and vigilance

Taking an ethological approach, habituation enables organisms to pursue their activities in the presence of pain while remaining vigilant, interrupting ongoing activities as soon as the original stimulus or the environment changes. So, in contrast to habituation to neutral stimuli, habituation to pain may be highly specific and easily disrupted. The 'primary task paradigm' [8,12] may be an interesting procedure to investigate this idea. In this task, individuals have to ignore pain to perform a cognitive task. Degradation in task performance (speed and accuracy) during pain is an index of task interference by pain. Using this paradigm, Crombez et al. [9] showed that task interference due to pain habituated over time, but – importantly - did not completely disappear, as it did for neutral stimuli. Previous studies have suggested that habituation to pain is easily disrupted by, for instance, changing the content of the procedure [21]. Future studies could further investigate this by focusing on *dishabituation*. We hypothesize that dishabituation of task interference might more easily occur to pain than to neutral stimuli. Pain duration may also be an important factor [48]: future research might investigate whether pain stimuli of short versus long duration differentially affect habituation.

## 4.2 Temporal and spatial context

Habituation of responses to pain may not only be dependent on sensory characteristics of the stimulus, but also on the context in which it appears. Changes in time and space can easily disrupt habituation to pain. Hardy et al. [21] described how, when habituation of the responses to pain had been achieved, “these same pains, if evoked under certain other conditions, were again evaluated as threatening and responses were then elicited” (pp. 279-280). For example, if experiments were conducted in a state of anxiety (e.g. during the preparation of material for a scientific meeting) or if the location of the painful stimulation was changed or expanded, responses increased again. We can therefore expect that habituation of responses to pain in one context will be very unlikely to generalize to another context. Importantly, we would expect habituation to pain to be more strongly dependent on the spatial and temporal context than neutral stimuli, with a small change in the context resulting in an increase of the response. Long-term habituation would then only occur when the context remains identical.

## 4.3 Indirect learning

Habituation can be the result of social learning from conspecific alarm signals [10,19,29,31]. This enables animals to learn about threatening events that they have not encountered before. Learning may be faster and more robust in species in which alarm behavior reliably predicts high threat. From an early age we learn which stimuli are potentially harmful and which are not by observing responses, such as facial expressions, of other individuals, particularly caregivers. Unlike non-human animals, humans can also learn through language [22]. Research investigating the influence of indirect learning on repeated painful stimulation is largely lacking [11,14,42]. It would, for example, be interesting to investigate whether manipulating the verbal description of painful stimuli in terms of bodily harm delays habituation.

## 4.4 Individual differences

Individual differences in habituation of responses to pain are found in humans, with some individuals showing a complete abolition of pain, whereas others continue to experience pain, though to a lesser extent, or even show sensitization. Some of these differences are presumably associated with psychosocial variables, such as stress, anxiety or negative affect. Under stressful situations, habituation of responses to pain might not easily occur. This would be consistent with the finding that brain structures implicated in pain habituation, such as the rostral anterior cingulate cortex and insula [3,42], are also involved in the processing of affective aspects of pain [39] and anxiety and stress [25,46]. Few studies have focused on individual differences in habituation of responses to pain (e.g. [1,5,17,33,44,47,62,63]). Individual differences may play a more important role in habituation to pain than in the initial response to a painful stimulus.

## 5 Future directions

### 5.1 Methodological implications

The focus on habituation in pain research has *methodological* implications. First, habituation must be considered as a confounding explanation for findings in some often-used paradigms in which painful stimuli are repeatedly applied (e.g. conditioned pain modulation (CPM), fear conditioning and exercise-induced analgesia). For example, stronger fear responses to signals of pain in patients in comparison with healthy volunteers may simply reflect a reduced habituation to painful stimuli in patients [27].

Second, most studies merely describe an attenuation of the response to painful stimuli after repeated stimulation, but do not address the characteristics of habituation, such as dishabituation (e.g. [7]). There is a need for studies that systematically investigate the characteristics of habituation to pain to compare with habituation to stimuli in other modalities.

Third, habituation may be assessed by any output of the nervous system. In the context of pain this is usually the self-report of pain, skin conductance response, nociceptive flexion reflex or evoked potentials. However, within a single individual the various 'output' channels do not necessarily converge (e.g. [26]). Researchers need to be aware of this and to gather data from more than one channel. Based upon the motivational-ethological perspective, we would expect habituation of behavioral disruption by pain rather than self-reported pain. We propose the primary task paradigm as an experimental analog of a real-life situation in which individuals must maintain their normal daily activities and pursue their valued goals despite pain.

Fourth, large inter-individual differences in habituation to pain exist (e.g. [45,52]). Whereas some individuals may habituate to stimuli of a certain intensity, others may not. We recommend systematically investigating heterogeneity in habituation and sensitization, for example by the standard use of mixed regression analyses [60].

### 5.2 Theoretical implications

The motivational-ethological framework on habituation of responses to pain provides a new *theoretical* perspective to guide future research. This framework emphasizes the importance of habituation to pain and explains *why* we habituate to pain. Habituation to pain should occur when the painful stimuli do not pose a threat, so it is adaptive to habituate to pain and to pursue valuable goals despite pain. Notwithstanding, habituation to pain should remain specific to characteristics of stimulus and context, and should be easily reversed. The motivational-ethological perspective stresses the *context* in which the behavior occurs, both spatio-temporal environment as well as social

context of the individual. In particular, in humans, the role of language in habituation seems a promising avenue for future research.

The motivational-ethological framework somewhat resembles cognitive-representational theories (in particular, [64]) that integrate non-associative and associative learning processes. However, whereas these models focus on *when* and *how* habituation occurs, the motivational-ethological perspective focuses on *why* habituation occurs. Within the motivational-ethological perspective, the presence of a memory trace is insufficient to produce habituation. Instead, this framework predicts that the *threat value* of the stimulus for the individual and the presence of *competing demands* will have an important impact on habituation. Of further interest, the motivational-ethological perspective posits that responding to stimuli may differ depending on which motivational system is activated (e.g. defensive vs. recuperative system [4]).

### 5.3 Clinical implications

Examining habituation to pain from a motivational-ethological perspective has some clinical implications. An inability to habituate to pain or a fast disruption of habituation (dishabituation) may foster chronic pain problems [3]. Several studies have found that certain pain types, such as fibromyalgia [47,56,57], migraine [2,16,51,58,59] and chronic low back pain [15,37,43,61], are characterized by deficits in habituation to pain. Future research needs to unravel whether the attenuation of habituation in chronic pain patients stems from deficits in sensory processing and/or from deficits in contextual processing, for instance by activation of responses to pain in inappropriate contexts. Some chronic pain conditions are characterized by ‘hypervigilance’ to pain [24], the tendency to attend to somatic distress signals [6]. We argue that hypervigilance may also result from an attenuation of habituation to pain. For example, Naliboff et al. [34] showed that hypervigilance to experimental visceral stimuli in patients with irritable bowel syndrome gradually normalized after repeated testing over 12 months. Identifying biological and psychosocial variables that are associated with individual differences in habituation to pain may shed more light on the processing of pain in general and, in particular, on the development of chronic pain.

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Table 1. The ten characteristics of habituation [40].

<b>Characteristic</b>	<b>Description</b>
#1 Properties of response decrement	Repeated application of a stimulus results in a progressive decrease in response to an asymptotic level.
#2 Spontaneous recovery	If the stimulus is withheld after response decrement, the response recovers at least partially over time.
#3 Potentiation	After multiple series of stimulus repetitions, the response decrement becomes successively more rapid and/or more pronounced.
#4 Frequency	Other things being equal, more frequent stimulation results in more rapid and/or more pronounced response decrement, and more rapid spontaneous recovery.
#5 Intensity	Within a stimulus modality, the less intense the stimulus, the more rapid and/or more pronounced the response decrement. Very intense stimuli may yield no response decrement.
#6 Habituation beyond asymptotic level	The effects of repeated stimulation may continue to accumulate even after the response decrement has reached an asymptotic level.
#7 Stimulus specificity/generalization	Within the same stimulus modality, the response decrement shows some stimulus specificity.
#8 Dishabituation	Presentation of a different stimulus results in an increase of the decremented response to the original stimulus.
#9 Habituation of dishabituation	Upon repeated application of the dishabituating stimulus, the amount of dishabituation produced decreases.
#10 Long-term habituation	Some stimulus repetition protocols may result in response decrement that last hours, days or weeks.