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Respondent learning in chronic pain: how precise is imprecision?

Letter To Editor:

We read the topical review by Moseley and Vlaeyen[11] with great interest. The authors propose "a new hypothesis of chronic pain," termed the "imprecision hypothesis" that "explains the most common painful disorders."

This hypothesis builds on classical conditioning and consists of 2 primary assumptions: (1) pain can be a conditioned response (CR) to initially neutral conditioned stimuli (CS) that are associated with initial painful events (unconditioned stimuli [US]); (2) the degree of generalization of such a CR to other stimuli depends on how precisely a "multisensory and meaningful event" during initial pain was encoded. In chronic pain, this encoding is assumed to be imprecise, leading to dysfunctional, exaggerated generalization.

Although we agree that both concepts contribute to chronic pain, we cannot concur with the authors that these are novel concepts. The role of classical conditioning in chronic pain is textbook knowledge. More than 35 years ago, Gentry and Bernal[4] proposed a stimulus–response model of the maintenance of chronic pain: acute pain leads to muscular tension, which in turn increases the pain experience. This sets a pain-tension cycle in motion that is complemented by avoidance, immobility, fatigue, and anxiety. Lethem et al.[8] specifically proposed that fear of pain may lead to avoidance and exaggerated pain perception.

Linton et al.[9] further elaborated the role of neutral stimuli in pain: a nociceptive stimulus (US) leads to pain that is accompanied by sympathetic activation, tension, and fear (unconditioned responses), which become associated with neutral stimuli present during the incident (CS). These CS then elicit arousal, muscular tension, and anxiety as CRs. The CRs facilitate the perception of a secondary pain, which may be of a different type than the original US.

Flor et al.[3] expanded this model to all levels of the pain response, including central processes.

Moseley and Vlaeyen write that their "idea is fundamentally different to the large body of work on aversive conditioning". Indeed, there is a difference: while classical accounts assume that pain-related responses, not pain, are the CRs, they propose "to extend this associative learning framework of pain-related fear to an approach that has pain itself as the response". However, all previous models considered pain as the end product of the conditioning process. That the pain itself is an immediate CR, however, is arguable. Linton et al.[9] concluded that "the conditioned response (CR) is not "pain," but it can be pain provoking." However, classical conditioning influences pain perception and can bring innocuous stimuli into a painful range (cf. Refs. 1,12).

Moseley and Vlaeyen hypothesize that more stimulus generalization occurs if the "encoding" of acute pain is "imprecise". The authors assume that this is the case in chronic pain. However, they do not clarify the mechanisms of such "encoding" and the meaning of "imprecise". The given examples for "imprecision" in chronic pain range from widespread pain to impaired tactile acuity and proprioception, cortical reorganization, and distorted mental body representations. Yet, these examples relate to very different levels of pain-related perception and it is likely that they stem from altered percepts due to learning-related modulatory processes that have been well described in perception and learning.

A relationship between perception and generalization has been shown in learning theory. For example, the "inverse hypothesis" by Guttmann and Kalish[6,7] states an inverse relationship between stimulus discrimination and generalization: the less an organism is able to discriminate stimuli, the stronger is the generalization. However, this hypothesis refers to the CS, not to the CR. At present, we do not know whether discrimination ability is reduced with respect to the CR and how this relates to generalization and chronic pain. Moreover, emotional, motivational, and cognitive processes likely also play a major role in generalization.[5]

In summary, the mechanisms of conditioning and generalization described in the "imprecision hypothesis" are important, but not novel, concepts in the understanding of chronic pain. That pain can result from conditioning has been discussed before. The term "imprecision" lacks precision. It might be more fruitful to investigate perceptual, emotional, cognitive, and motivational processes related to learning and pain within existing conceptual frameworks. Finally, it is unlikely that the primary disturbance is in the acquisition of pain-related responses, which is crucial for survival. Rather, extinction might be most important for chronicity processes.[2] We commend the authors for putting a new focus on respondent learning processes in pain, complementing operant learning accounts[10] and hope for a new focus of research on learning processes involved in chronic pain.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Reply

Letter To Editor:

We were pleased to see the letter[8] regarding our recent article on the Imprecision Hypothesis of chronic pain.[22] We proposed that generalization of pain as a conditioned response to the non-noxious suite of inputs first associated with noxious input might provide a mechanism by which acute pain transitions into a chronic pain disorder.[2] The letter highlights the historical and empirical foundations of this idea and the challenges that we face in interrogating it. The letter also reinforces the novelty of this idea and its dependence on a different, albeit firmly established, conceptualization of pain itself.

We wholeheartedly agree that the Imprecision Hypothesis builds on several fundamental and established concepts, and we are mortified to think we would not give due respect to the massive amount of work in pain-related conditioning. However, as Fuchs et al. astutely observe, previous theorists have posited that classical conditioning mechanisms modulate pain through an "indirect" pathway, such as sympathetic arousal, muscle reactivity, and pain-related fear. Indeed, Fuchs et al. have made critical contributions to that body of evidence, and we are among many who have gratefully integrated those concepts into research approaches such as interoceptive[5] and proprioceptive fear conditioning paradigms[15] and cross-sectional patient–control comparisons.[10] We also have integrated these ideas into our treatments, eg, "addressing the output systems" component of Explaining Pain,[18] and exposure-based treatments for individuals reporting increased pain-related fear.[4]

Fuchs et al. assert "that pain itself as an 'immediate' conditioned response is arguable," also quoting the book chapter by Linton et al.[13] from 30 years ago—"the conditioned response is not pain, but it can be pain provoking,"—sentiments that Fordyce was proposing even earlier.[6] Those assertions not only highlight the novelty of the Imprecision Hypothesis but also point to its integration of a fundamentally different conceptualization of pain: that of a perceptual inference[7] that motivates protective behavior, rather than serving as a readout of nociceptive input or tissue dysfunction. The idea that previous information about features of a stimulus modulates its perception is clearly a shift from that used in pain-related conditioning studies, but it is not a novel idea in itself.[7,11] The idea that we are proposing imprecise encoding of the conditioned response, unfortunately, is a misinterpretation of our thesis; we actually propose imprecise encoding of the conditioned stimuli, as per the inverse hypothesis.[9] This misinterpretation is a common misunderstanding when pain is conceptualized as an input and the brain as a "receipt organ," rather than conceptualizing pain as an output[17] or perceptual inference. We regret that we did not clearly articulate this, and the letter serves as a reminder to do better.

We agree with Fuchs et al. that a number of challenges must be overcome if we are to comprehensively interrogate the Imprecision Hypothesis. Empirical evidence for the idea that pain can be a conditioned response is still lacking, and the circumstances under which such conditioning may occur are yet to be identified.[3] Also, research on stimulus generalization has a long history in both Pavlovian and instrumental conditioning and is currently enjoying an extensive revival. Its application in the area of pain[14] is more recent, however. As Fuchs et al. correctly noted, we need to reveal how complex sensory events are encoded in the first place and what the neurophysiological correlates of imprecise encoding are. Imprecise encoding not only can foster generalization but also alter perceptual memory consolidation and retrieval.[12]

We are making ground amidst these challenges; the examples we provided (for instance, imprecise cortical maps of touch[2] or proprioception[1,23] in people with pain [see also Refs. 21,25 for reviews] and expansion of disrupted body parts to spatial zones[19,20]) have been very useful starting points for our investigations. An exciting avenue is that pain modulation can also be rooted in altered perceptual decision-making.[16,26] Nonetheless, much needs to be learned, not least being the contributions of emotional, motivational, and cognitive processes.

In summary, we are pleased that Fuchs et al. share our enthusiasm for a new focus of research on learning processes associated with chronic pain and we welcome the opportunity to clarify aspects of the Imprecision Hypothesis. We acknowledge that there is a large body of work that describes an indirect end organ/output system–mediated pathway by which conditioning might exacerbate pain, and we consider that the massive literature on conditioning, on which the Imprecision Hypothesis is grounded, is actually one of the strengths of the hypothesis. We accept that conceptualization of pain as an output or perceptual inference is counter to the dominant conceptual viewpoints in the pain-related conditioning literature, but we also acknowledge that this "new" conceptualization is actually not that new.[24] Finally, we contend that the development of new conceptual frameworks can be helpful if they are grounded in established principles and are in line with current theoretical concepts in the field.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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