Topical Review

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Beyond nociception: the imprecision hypothesis of chronic pain

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Chronic pain is the most burdensome health issue facing the world today; its cost to Western countries is comparable with that of diabetes and cancer combined.[21] Our understanding of the pathophysiology of chronic pain has increased substantially over the past 20 years, including but not limited to changes in the brain.[23] However, we still do not know why chronic pain develops in some people and not in others, although we do know that the type or extent of their injury, personality, occupation, postcode, education level, race, or religion are not strong predictors.[6] Extensive research into the genetics of chronic pain has also thus far been underwhelming, perhaps because too many genes are involved and results are conflicting.[12] Chronic pain is very difficult to treat; 60% of those with chronic pain will still be in pain after 1 year.[7] It seems that despite extensive advances in multiple fields, we have made little ground. In this topical review, we put forward a new hypothesis of chronic pain that explains the most common painful disorders, such as chronic widespread pain, nonspecific back or neck pain, and fibromyalgia. Our hypothesis draws on a long history of fundamental research in associative learning and is based on 2 core assumptions (1) that pain can be considered a response, not just a stimulus, and (2) that encoding non-nociceptive information predictably coincident with nociceptive input underpins the response to subsequent similar events. Briefly, our hypothesis posits that the precision with which multisensory information (temporal, proprioceptive, spatial) about the painful event is encoded and represented in the brain will determine the degree to which the painful response will subsequently generalize to similar events.

Much of the literature on pain considers it analogous to nociception, activity in high-threshold afferent neurons and their central projections. However, a very large body of evidence demonstrates that nociception is neither sufficient nor necessary for pain (see Refs. 4,11,22). Pain is now considered a conscious experience that can be, and often is, associated with nociception, but it is always modulated by a myriad of neurobiological, environmental, and cognitive factors. Plasticity, or the alterations in stimulus–response patterns that occur over time, is thought to be important in chronic pain and can occur in at least 2 ways. One is nonassociative when the organism's response to a stimulus changes by virtue of repeated exposure to that particular stimulus. Habituation is 1 example of nonassociative plasticity, such that the response to a given stimulus decreases. Sensitization is another example, such that the response to a given stimulus increases. Sensitization of spinal nociceptors is considered a key mechanism underpinning persistent pain after primary nerve trauma or dysfunction; repeated noxious stimulation leads to a shift in the stimulus–response pattern of the spinal nociceptor.

A second arguably more complex form of plasticity involves the association of at least 2 stimuli, such is the typical case of classical (Pavlovian) conditioning or associative learning.[16] Associative learning concerns the acquisition of propositional knowledge about the relationship between 1 stimulus and at least one other. When no special conditions are necessary for a given stimulus to elicit the response, the stimulus is said to be "unconditioned." Pairing a biologically relevant unconditioned stimulus (US) with a neutral conditioned stimulus (CS) usually results in the CS acquiring motivational properties. That is, the CS comes to elicit responses that are similar to the responses elicited by the US. These new responses to the CS are therefore called "conditioned responses" (CR). In the vast majority of associative learning research involving pain, pain is considered a US that activates an immediate defensive response, most obviously fear. Thus, fear is considered the unconditioned response (UR). Pairing pain with a previously neutral CS, for example a given auditory tone, leads to that neutral CS eliciting the same defensive response, now called a CR.

This paradigm is well established in emotion research, where it is called fear conditioning, and it forms the underpinnings of a prevailing model of the development of pain-related disability, the fear-avoidance model.[9,17,19,20] In that model, otherwise neutral stimuli, for example, certain activities that predict the occurrence of pain begin to elicit fear responses in the anticipation of pain and thus also in the absence of pain. Not surprisingly, this elicitation leads people to avoid those activities and, hence, the descending spiral of inactivity and disability.

We propose to extend this associative learning framework of pain-related fear to an approach that has pain itself as the response, rather than the stimulus. To understand that our idea is fundamentally different to the large body of work on aversive conditioning, one must discard the Cartesian view that our percepts are simply readouts of sensory input and understand the distinction between pain and nociception. In fear-conditioning studies, pain is used as a stimulus and defensive reactivity (eg, avoidance behavior, increased arousal, selective attention) is considered the response.[19] Here, we suggest that pain can also be a response. Our hypothesis considers the nociceptive input as the US, for which there are no special conditions necessary to evoke pain, the UR. The multisensory and meaningful events that

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routinely coincide with, or preempt, the nociceptive input are the CS. With repeated association, the CS comes to elicit pain, which is therein considered the CR (**Fig. 1**). Once the nociceptive and non-nociceptive inputs are associated, a process termed "acquisition," not just the initial multisensory event will elicit the painful response but also events that share some features with that multisensory event. This process is called stimulus generalization. Stimulus generalization is negatively related to the degree to which 1 stimulus can be differentiated from another functionally distinct stimulus. This stimulus differentiation is essential to optimize behavioral specificity.[8,16]

Applying this fundamental tenet of Pavlov's work to a multifactorial percept such as pain, we can consider that the extent of generalization is negatively related to the precision with which the original painful event is encoded by the brain. The more "blurred" the encoding, the more generalization occurs and the more likely it becomes that pain will be triggered by more functionally distinct stimuli (**Fig. 2**). That is, imprecise encoding of the original painful event, which may be, for example, bending forward, results in generalization of back pain to similar movements and activities. This mechanism actually offers a biological advantage because it affords a buffer of protection. However, at some point of generalization, the protective function moves from being adaptive or helpful to being maladaptive or unhelpful.

The Imprecision Hypothesis offers a novel and more precise way of conceptualizing the dominant clinical presentation of chronic pain, that of the gradual development of pain, which becomes triggered by a widening array of movements, activities, and stimuli, most notably evidenced in chronic, widespread "nonspecific" pain. The Imprecision Hypothesis is both falsifiable and testable. Critically, there is a large body of knowledge in the field of associative learning that can be applied to test predictions made by our model. The Imprecision Hypothesis is also biologically plausible. In acute pain, activation of nociceptors during particular movements or behaviors predictably increases pain. However, just as visual stimuli are encoded as integrated and meaningful object percepts, not as an array of individual object features or simply a retinal "impression"[10] (as evidenced by compelling illusions such as the Necker cube[15]), so too are painful movements and behaviors encoded as integrated multisensory and meaningful events, not simply as a nociceptive "impression" or barrage. Such integrated percepts present an excellent situation for associative learning, which permits rapid triggering of protective responses and sophisticated non-nociceptive mechanisms.

How different is the Imprecision Hypothesis from the concept of central sensitization? The key difference is that central sensitization has been attributed to entirely nonassociative mechanisms. Even regarding allodynia, where non-nociceptive input triggers pain, no import is given to the previous association between nociceptive and non-nociceptive input. Indeed, what is currently known about central sensitization attributes it to sprouting of non-nociceptive primary neurons induced by death of nociceptive neurons, for example after peripheral nerve injury, or to heterosynaptic facilitation induced by ongoing primary nociceptor input, descending facilitation, or both.[24] That is, that nonnoxious stimuli come to trigger nociceptive input, manifest in allodynia, hyperalgesia, and spreading of receptive fields is

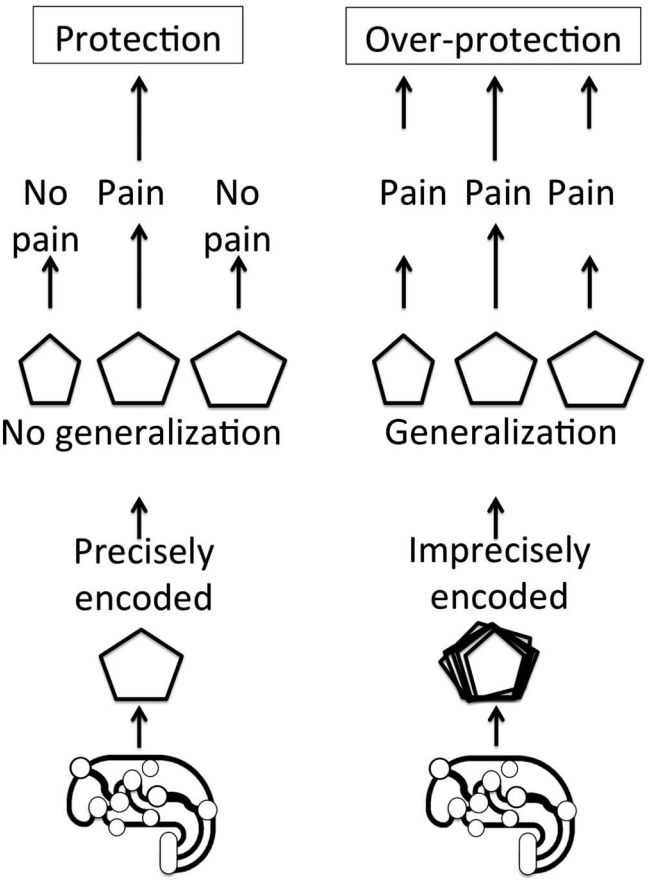

Figure 2. Left panel: Precise encoding by the brain of the multisensory and meaningful event leads to no generalization such that the organism is protected only from the multisensory event that has been associated with nociceptive input. Right panel: Imprecise encoding of the multisensory event leads to generalization such that the CR, pain, is also triggered by events that share some features with the conditioning multisensory event. Note that some degree of generalization is biologically advantageous, but overgeneralization will manifest in a wide array of triggering events, allodynia and hyperalgesia, such as is observed in the vast majority of chronic pain states. That is, overgeneralization leads to pain being evoked by events that are not in fact dangerous, and the organism becomes "overprotected." CR, conditioned response.

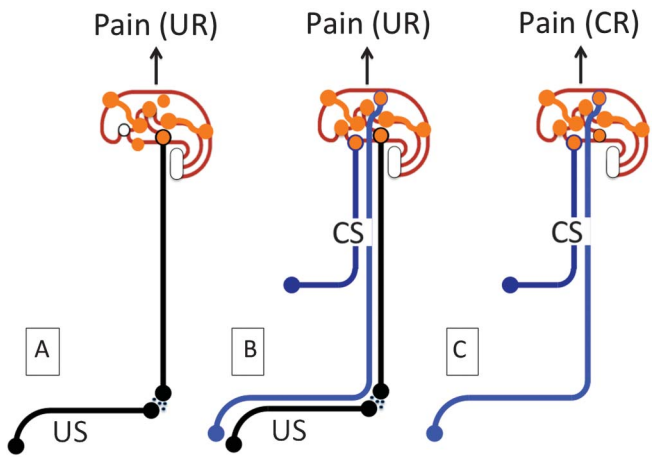

Figure 1. Associative learning of pain. (A) The nociceptive input is the US that will usually elicit pain, which is the UR. (B) The multisensory and meaningful events that routinely coincide with, or preempt, the nociceptive input can be considered the CS. (C) Through established processes of associative learning, the CS comes to elicit pain, which is therein considered the CR. US, unconditioned stimulus; UR, unconditioned response; CS, conditioned stimulus; CR, conditioned response.

thought to depend on sprouting of primary non-nociceptive afferents or sustained activation of the spinal nociceptor, not association between nociceptive and non-nociceptive input.[24] Importantly, associative learning and central sensitization are not necessarily mutually exclusive, but both would manifest in clinical signs such as allodynia and hyperalgesia.

A great deal of clinical and experimental data is consistent with the Imprecision Hypothesis, although they do not prove it. For example, widespread pain is characterized, indeed diagnosed, by a wide array of pain triggers that gradually develop over time.[1] A growing body of literature documents imprecision in bodily cortical representations in people with chronic pain. For example, somatotopic imprecision, most clearly captured clinically in reduced tactile acuity in the painful area, is characteristic of a range of chronic pain states and is not explainable by deficits in transformation of the stimulus or transmission of the sensory signal[5]; spatial and proprioceptive aspects of multisensory events are encoded less precisely in people with chronic pain than they are in people with acute pain or in healthy controls; the cortical representation of non-nociceptive stimuli is disrupted in people with chronic pain, a phenomenon widely termed "cortical reorganisation"; people with chronic pain have lower proprioceptive acuity, disruptions in the perceived size and alignment of body parts, and show poor ability to mentally maneuver the painful body part (see Refs. 4,13,14,23 for reviews). Critically, these deficits are not body-wide, although they do extend to various extents beyond the region of pain (eg, see Ref. 18), and these deficits cannot be explained by behavioral factors, tissue injury, ectopic firing of primary nociceptors, or central sensitization. Finally, these problems are not explained by deficits of working memory or executive function, although both are more common in people with chronic pain than they are in healthy controls.[2,3]

In summary, the Imprecision Hypothesis posits pain as a CR to the multisensory and meaningful events that routinely coincide with, or preempt, nociceptive input. Moreover, imprecise encoding of those multisensory and meaningful events leads to overgeneralization of the response, such that an adaptive and protective process becomes maladaptive, distressing, and disabling chronic pain. The idea represents a new framework against which clear and predictable experimental hypotheses, themselves drawn from a massive literature on associative learning, can be tested. Much of what we currently know about pain and the course of chronicity after an acute episode is consistent with our hypothesis. Much of what we currently know about the differences between people who have developed chronic pain after an initial injury and those who have not is consistent with our hypothesis. Experimental and longitudinal studies are clearly required, and if we are correct, it will open up new possibilities for the treatment of people with acute pain, focusing not on distraction and analgesia but on precisely encoding the painful event. The extant literature on motor learning, spatial attention, sensory training, and neuroplasticity should provide a valuable base on which to embark on such a task.

Conflict of interest statement

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