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Learning to predict and control harmful events: chronic pain and conditioning

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Abstract

Pain is a biologically relevant signal and response to bodily threat, associated with the urge to restore the integrity of the body. Immediate protective responses include increased arousal, selective attention, escape, and facial expressions, followed by recuperative avoidance and safety-seeking behaviors. To facilitate early and effective protection against future bodily threat or injury, learning takes place rapidly. Learning is the observable change in behavior due to events in the internal and external environmental and includes nonassociative (habituation and sensitization) and associative learning (Pavlovian and operant conditioning). Once acquired, these knowledge representations remain stored in memory and may generalize to perceptually or functionally similar events. Moreover, these processes are not just a consequence of pain; they may directly influence pain perception. In contrast to the rapid acquisition of learned responses, their extinction is slow, fragile, context dependent and only occurs through inhibitory processes. Here, we review features of associative forms of learning in humans that contribute to pain, pain-related distress, and disability and discuss promising future directions. Although conditioning has a long and honorable history, a conditioning perspective still might open new windows on novel treatment modalities that facilitate the well-being of individuals with chronic pain.

Keywords: Chronic pain, Conditioning, Learning, Avoidance, Behavior, Extinction, Generalization, Discrimination, Exposure

1. Introduction

Pain is an unpleasant sensory and emotional experience that urges the individual to take action to restore the integrity of the body. Eminent theorists see pain "… as a syndrome where pain and the associated emotion are 2 faces of the same coin." [Wall 1979, p. 256]. Pain is an emotional response emitted when specialized sensory fibers that innervate peripheral tissues are activated by noxious stimuli.[117] Pain is also a motivational state that initiates early defensive behaviors followed by recuperative behaviors and which has the primary function to promote recovery from injury.[10,111] Given its intrinsically alarming nature, accurate prediction of the occurrence of pain and to minimize its outcome takes priority. Prediction can be realized by the detection of cues that precede the occurrence of pain and bodily threat, so that their impact can be avoided. However, pain cannot always be avoided, and some pain-related behaviors may only result in the temporary relief of pain and associated suffering. In a dynamic and continuously changing environment, prediction errors may occur, requiring rapid adjustments of individual's responses to similar stimuli. Fortunately, the plasticity of the peripheral and central nervous system allows swift behavior changes.[96] Learning (or conditioning) is the observable change in behavior because of changes in the internal and external environment.[82] The term "conditioning" is here used as a particular form of learning and not to be confused with conditioned pain modulation (CPM). In CPM, simultaneous exposure to 1 (conditioned) painful stimulus reduces the intensity of a second (test) stimulus.[119]

There are 2 forms of learning: nonassociative and associative. In nonassociative learning, a behavior change can be observed as a result of repeated encounters with a single stimulus (**Fig. 1A**). Habituation is a decrease, whereas sensitization is an increase in the strength of responding to a single stimulus because of repeated exposures to that stimulus. The reasons why repeated presentations of a stimulus result in either habituation or sensitization are still unknown, but there is preliminary evidence that the repeated exposure to intense and unpredictable stimuli more likely leads to sensitization rather than habituation.[78,90,115] Associative learning occurs when the response to a stimulus changes as a result of the particular pattern of co-occurrence between 2 or more stimuli, or between a particular behavior and subsequent stimuli, and allows the organism to shape an accurate representation of the internal and external environment. Pavlovian (or classical) conditioning is the learning of relations among events, making it possible to *predict* the occurrence of potentially harmful stimuli in that environment.[81,87] Operant (or instrumental) conditioning is the learning about actions and their consequences, during which the behavior changes as a result of the value of the stimulus (or stimulus change; the outcome) after that behavior. Operant conditioning allows the individual to *control* potentially harmful events.[11,102] Here, we will review features of associative forms of learning in humans that contribute to pain, pain-related distress, and disability, and suggest promising avenues for future research in this area.

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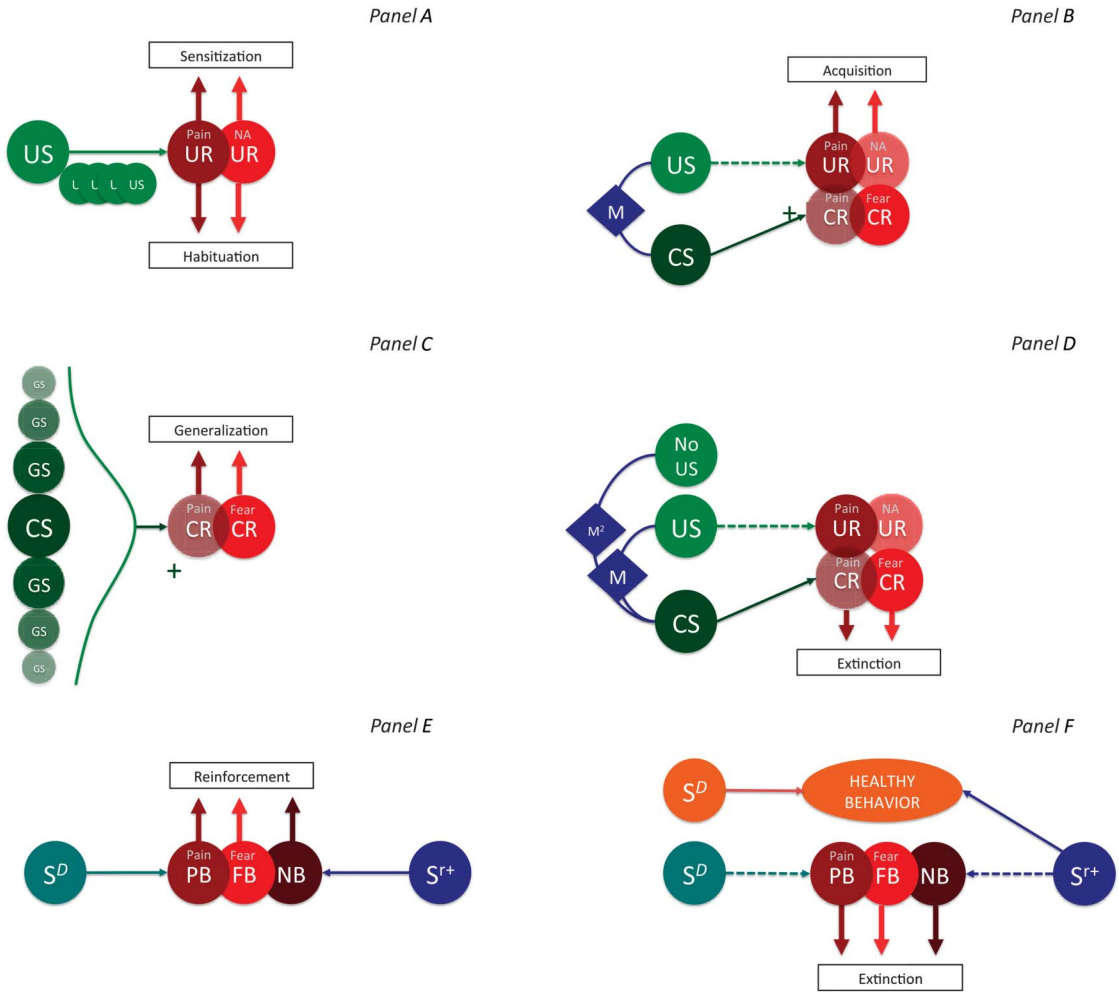

Figure 1. Graphical presentations of processes of nonassociative and associative conditioning. (A) Sensitization and habituation, (B) Pavlovian acquisition, (C) Pavlovian generalization, (D) Pavlovian extinction, (E) operant reinforcement, (F) operant extinction through differential reinforcement of healthy behavior. US, unconditioned stimulus; UR, unconditioned response; NA, negative affect; CS, conditioned stimulus; GS, generalizing stimulus; CR, conditioned response; M, memory trace; PB, pain-related behavior; FB, fear-related behavior; NB, any novel behavior; S^D, discriminative stimulus; Sr+, positive reinforcement.

2. Pavlovian conditioning and pain: predicting potential harm

Gathering propositional knowledge about the relationship between 2 events or stimuli, of which one is relatively neutral in terms of its biological meaning (the conditioned stimulus; CS) and one that is biologically more relevant and potent (the unconditioned stimulus; US), is the core of Pavlovian conditioning (**Fig. 1B**). The US is a centrally detected disruption of the usual environment, and the set of behaviors that aim at restoring the homeostasis is the unconditioned response (UR).[86] During Pavlovian conditioning, CS–US associations are stored in memory by virtue of which an encounter with the CS activates the representation of the US and hence elicits a conditioned response (CR) that is similar to the UR. Through the repeated CS–US associations, the CS has changed its meaning, from a neutral event that can easily be disregarded to a cue that might predict the US and which requires motivational priority. As the CR usually includes the avoidance of the US, the individual is left with the memory representation of the US only, which may be vulnerable to cognitive distortions. The associative strength between CS and US does not depend only on actual pairings of the CS and US but also on other relevant events, such as environmental context, verbally and culturally transmitted information, existing beliefs, and emotions elicited by the CS.[24] According to the Rescorla–Wagner model, Pavlovian conditioning is the acquisition of an *expectancy* of a salient event, of which the associative strength is controlled by the salience of the stimuli, and the difference between the actual vs the expected intensity of the US.[88] After such a "prediction error," behavior will be adjusted according to the corrected US predictions.[83] Later on, more dynamic temporal difference models have been introduced,[99] which allow for the prediction of sequential learning outcomes and include (temporal) prediction errors already before the occurrence of a particular US.[96]

Applied to pain, nociceptive input and the associated nociceptive sensation is a disrupting event that can be considered a US that is usually associated with pain, containing both a sensory and a negative affective component.[54,111] The sensory component is related to pain discriminability and intensity. According to Price's multistage model of pain processing,[84] the affective component consists of an immediate pain unpleasantness associated with the sensory features of the pain felt, fueled by the perceived intrusion or threat (eg, distress, annoyance, fear). In a subsequent stage, a more future-oriented negative affect (eg, depression, frustration, anger, anxiety) subsists from the threatening long-term consequences of the nociceptive input (eg, interference with valued life goals). Psychophysiological arousal (increased muscle tone, skin

conductance, startle), interruption of ongoing activity, selective attention, escape (including withdrawal reflexes), and altered facial expressions are typical examples of immediate and defensive pain-related URs that are usually followed by recuperative behaviors such as inactivity, avoidance, and safety-seeking behaviors (when escape or avoidance is not possible).[10] The strength of the UR may vary, and individuals whom by their learning history report pain to be highly threatening emit stronger unconditioned pain responses.[80,95,98] Prolonged avoidance and safety behaviors are assumed to be critical for the development of chronic pain.[4,57,105]

CSs are neutral stimuli that precede or concur with the nociceptive input, and they can be exteroceptive (tactile, visual, auditory), interoceptive (visceral, olfactory), or kinesthetic/proprioceptive (change of position).[16] Once the expectancy of nociceptive input and its mental representation is acquired, pain-related fear and associated defensive behaviors as CRs will be activated. Their function is to minimize future encounters with the noxious event. Although animal research has shown that there is a direct central inhibition between both the pain and fear motivational systems (fear inhibits pain), research in individuals with chronic pain has shown the contrary, namely, that fear lowers pain thresholds and tolerance (fear enhances pain). There may be several reasons for this. First, in human research, the US is never life threatening, and fear may not reach the necessary level to execute its (endogenous opioid-mediated) inhibitory function. Second, pain-related fear is associated with worrying about the origin and possible control of prolonged pain that may induce negative affect causing (sympathetically mediated) sensitization.[49] Third, fear may emerge as a conditioned form of pain, where pain is the US and fear the CR.[106]

Because of their relative ease to use, most Pavlovian conditioning studies use exteroceptive (mostly visual) CSs and include pain-related psychophysiological reactivity and pain-related fear responses as the CRs. In 1 study, the color of a visual stimulus signaled the occurrence (CS+) or the nonoccurrence (CS−) of an electrocutaneous nociceptive stimulus. Participants responded with greater potentiated eyeblink startle, heightened skin conductance, and cardiac deceleration in the presence of the CS+, as compared with CS−, in the absence of the US.[12] Classical conditioning has also thought to be the underlying mechanism for the increased muscular reactivity often seen in chronic pain patients, which may prolong the symptoms.[36,93,108] Trace conditioning of the eyeblink reflex has shown to be enhanced in fibromyalgia patients.[76] Using a differential conditioning paradigm with auditory CSs, Klinger et al.[53] found that patients with chronic back pain and tension type headache showed URs to an intracutaneous nociceptive stimulus in lumbar and trapezius muscles significantly more often than the healthy controls. The number of substantial electromyographic (EMG) responses to the CS+ (a visual cue) was significantly higher than the number of responses to the CS−. Furthermore, a significant relation was found between conditioned muscular responses and the self-reported pain intensity 1 day after the experiment. Another study extended these results to neural activity and revealed that the CS+ not only led to fast acquisition and increases in muscle reactivity as measured with EMG but also changed the dipole orientation on the EEG, suggesting that the somatosensory cortex (SI) contributes to memory processes in associative learning. As predicted, the conditioned EMG response decreased when the tactile stimuli were not followed by nociceptive stimuli anymore.[29] Yáguez et al.[118] used colored circles as the CS and interoceptive esophageal distention as the US and showed that the conditioned visceral stimulus elicited similar cortical responses (anterior cingulate cortex, insula, primary and secondary somatosensory cortices, and insula) as the US.

Another series of experimental studies have attempted to classically condition the fear component of the UR. For example, conditioned anticipatory activations are seen in core areas of the central fear network including the amygdala and the anterior cingulate cortex in a conditioning study where visual stimuli were paired with interoceptive rectal distensions, and this paradigm might be an interesting model to better understand the etiology of chronic abdominal pain.[7,51] In an attempt to model fear of pain in musculoskeletal pain patients, Meulders et al. used passive joystick movements as proprioceptive CSs of which the direction predicted painful electrocutaneous stimuli to the hand as the US (eg, moving upward as CS+ and moving downward as CS−). As compared with a condition in which both movements were explicitly unpaired with the pain-US, the CS+ movement elicited increased fear of movement-related pain, larger eyeblink startle amplitudes, and slower movement latency responses than the CS−.[71] Interestingly, the mere intension to perform a painful movement was associated with similar conditioned responses (CRs).[74]

2.1. Stimulus generalization and discrimination

A particular feature of Pavlovian conditioning is that stimuli sharing characteristics with the original fear-provoking CS (so-called generalizing stimuli; GS) may become capable of eliciting similar CRs, following a gradient dependent on the perceptual or functional proximity between CS and GS (**Fig. 1C**). During *stimulus generalization*, individuals extrapolate knowledge from 1 situation to other situations without actually having to experience them. Generalization reduces the risk of missing positive alarms, but goes with the cost of an increased risk to responding to false alarms, and has shown to be a potent predictor of distress outside the pain field.[62] Generalization of pain-related fear has been suggested a mechanism contributing to the spreading of pain. In line with this idea, fear of pain prospectively predicted the experience of multisite pain after induction of delayed onset muscle soreness in healthy participants.[77] *Stimulus discrimination* is the degree to which the representation of 1 stimulus can be distinguished from that of other stimuli. In other words, the precision by which the representation of a stimulus is encoded or retrieved in memory is negatively related to the array of stimuli that can activate it.[75] Adaptive learning relies on a flexible balance of generalization/discrimination toward novel situations. Using the joystick movement paradigm in healthy subjects, we recently demonstrated a typical generalization gradient in eyeblink startle reflexes for novel movements that varied in similarity with the painful CS+ movement.[70,73] In patients with fibromyalgia, however, a nondifferential generalization was observed in FM. That is, all novel stimuli regardless of their perceptual resemblance to the original CS+ or CS− appeared to elicit strong conditioned fear responses.[68,69] This learning deficit might be involved in the maintenance of chronic pain, because potential danger and harm is not successfully identified, which leads to sustained anxiety and further fuels the spreading of fear and avoidance behaviors. In other words, it is perhaps not so much the intensity of the fear of pain response that is contributing to disability, but the (increasing) range of stimuli capable of predicting harm and hence eliciting the CRs that interferes with daily functioning. However, more experimental and longitudinal studies in individuals with chronic pain are needed to draw conclusions about the causal status of these learning deficits.

2.2. Extinction

When the US (or its mental representation) ceases to follow the CS, the latter loses its predictive value and, consequently, the CR extinguishes (**Fig. 1D**).[7,72] Extinction is a fragile process, as the original CS–US propositional knowledge remains stored in memory, also after gathering disconfirmatory evidence. Extinction is also context dependent, and CRs may return when the individual encounters a novel CS that is slightly different from the extinguished CS[22] (restricted generalization, but see also Ref. 103), or when the extinguished CS is encountered in a different context than the one where extinction took place (renewal).[61] Finally, an unexpected flair-up of pain-US (reinstatement) or a nonpain stressor US (cross-reinstatement) can easily reinstate pain-related fear.[31,43,74] Reinstatement is particularly relevant for patients with chronic pain, as these patients will—per definition—occasionally be exposed to pain exacerbations even after successful treatment. Although the underlying mechanisms are not known yet, context conditioning is very likely given that the US after extinction occurs in the absence of an explicit CS. Cross-reinstatement effects may also reflect the activation of old fears or the acquisition of a new fear.[97]

Exposure in vivo is the clinical analog of such an extinction procedure and has successfully been applied in patients with chronic musculoskeletal pain.[107] When individuals confront rather than avoid painful movement, they can readjust their predictions about the learned associations between movements and increased pain. Outcome studies have shown that exposure treatments are especially effective in reducing pain-related fear and the perceived harmfulness of physical activity,[56,59,114] and smaller trials with non–randomized controlled experimental designs also showed reduced pain reports and successful resumptions of personal goals.[26,27]

2.3. Future directions

Although Pavlovian conditioning is one of the oldest and most systematically studied learning processes in psychology, its application in pain research is more recent, which leaves many questions unanswered. Just a few are listed here: (1) Pain-related fear and psychophysiological correlates of pain can be conditioned, but how about pain responses that were not elicited by nociceptive input? Despite a number of efforts to classically condition pain, the results almost always reveal the amplification of pain in the presence of the CS at best but not the occurrence of pain.[113] There are only a few reports of pain sensations being felt when the subject was requested to imagine the CS after a Pavlovian acquisition procedure under hypnosis.[58] The conditions in which a neutral stimulus elicits a painful experience by virtue of previous associations between both stimuli still need to be uncovered, if at all possible,[20] and insights from the research on placebo/nocebo might be helpful here.[14,19] Besides its theoretical value, this knowledge might not only help us understand the occurrence of so-called spontaneous pain[116] but also to possible ways to extinguish conditioned pain responses. (2) There is good evidence to expect strong associative learning among stimuli that are functionally related. For example, interoceptive conditioning occurs when the CS is a natural precursor of the US or when the CS is a stimulus early in the causal chain of events that leads to the US. Studies on such homoreflexive conditioning are scarce but highly relevant in pain research,[28,30,79] and the development of interoceptive exposure treatments for chronic pain is on its way.[34] (3) Generalization of pain-related fear has been suggested as a mechanism contributing to the spreading of pain and might represent an associative learning mode for signs and symptoms that are usually associated with sensitization, although firm data are not available yet. Indeed, common consequences do not necessarily imply common mechanisms. The relative contribution of associative and nonassociative processes in generalization of pain-related fear and pain responses merits further investigation, especially given that it would extend the number of options for the extinction of dysfunctional CRs.[32] (4) Learning, prediction, and perception are closely tied. Perception currently is considered an inferential process in which prior information is used to interpret sensory information, often resulting in minimization of sensory prediction errors.[40,112] Evidence outside pain domain reveals that aversive learning increases perceptual discrimination thresholds,[89] and an intriguing question is how such perceptual biases in turn influence associative learning.[1,121] (5) Learning is dependent on a prediction error, but what happens if painful events remain perceived as unpredictable? Besides the disruptive[2] and hyperalgesic effects of uncertainty itself,[48,120] we suggest that unpredictable pain leads to a sustained prediction error signaling, perceptual widening, and possibly spreading of pain.[44] Although still speculative, it is a research area that merits further scientific attention. (6) Finally, there is a need to consider conditioning in a motivational perspective, where the goal to restore the integrity of the body is considered in the context of multiple goals.[21] Competing nonpain goals, goal conflicts, and individual differences in goal flexibility may inhibit or overrule pain avoidance goals.[18,67,94,104]

3. Operant conditioning in pain: controlling potential harm

Although operant conditioning is about the learning of actions and their consequences, there are many parallels between Pavlovian and operant learning in terms of rules or laws.[11] Operant conditioning is the modulation of behavior because of the learned association between behavior and subsequent meaningful changes in the environment, also called reinforcers (S^{r+}).[33] Such reinforcers can act not only on the more reflexive defensive and recuperative behaviors mentioned earlier but also on novel voluntary behavior the individual engages in to reduce suffering (**Fig. 1E**). Discriminative stimuli (S^{D}) are stimuli that precede operant behavior, and rather than eliciting a behavioral response they increase the likelihood or set the occasion for the behavior to occur.[82] In the early 60s, the American psychologist Wilbert Fordyce was one of the first to suggest that the development of chronic pain was mainly the result of external contingencies of reinforcement controlling observable "pain behaviors" (such as crying, limping, moaning, and using medications), thereby maintaining the pain problem beyond the expected healing time.[37,38] Fordyce considered the effects of behavior as "causes" of future action (in line with Thorndike's law of effect[102]) and identified 3 ways in which operant conditioning could maintain disabling pain behaviors: direct positive reinforcement (eg, social attention), negative reinforcement (escape/avoidance from noxious stimulation), or deficient positive reinforcement for "well behavior" (eg, praise for leisure activity, working). Most experimental studies have focused the first mechanism, leaving the 2 other mechanisms largely untested so far. The first preliminary studies manipulating positive reinforcement were promising.[8,15] Linton and Götestam[60] experimentally manipulated the consequences of pain behaviors in the laboratory. In 2 subsequent studies, they verbally reinforced healthy participants who were undergoing an ischemic pain test for increasing and decreasing

verbal pain reports. Despite failed replications,[63,64] more recent studies were successful in establishing operant learning of pain behavior. One study in which contingency awareness and participants' disposition to amplify body sensations was controlled for clearly showed operantly conditioned increases and decreases in verbal pain behaviors.[50] Flor et al.[35] were able to demonstrate that both chronic low back pain patients and healthy controls groups showed similar learning rates, but the patients displayed slower extinction of both the verbal and the cortical (N150) pain response. In addition, the patient group displayed prolonged elevated EMG levels. This study suggests that CBP patients may be more sensitive to operant conditioning than healthy controls, which may add to the maintenance of the chronic pain problem. Instead of verbal reports of pain, Kunz et al.[55] elegantly tested the operant modulation of facial expressions and found that facial pain behavior could be successfully up- or downconditioned. Interestingly, their results also showed that the decline in facial pain displays during acquisition also predicted changes in subjective pain ratings.

Another and perhaps more critical test of operant conditioning of pain behaviors is not by assessing the frequency of those behaviors during the presence and absence of reinforcers, but by testing whether pain behaviors are emitted in the presence of the S^D without S^{r+}. For example, when verbally expressing pain is positively reinforced by solicitous spouse responses, these pain responses are more likely to occur in the mere presence of the spouse as compared with other people even if she/he is not providing any reinforcement. This is what was found in an early study by Block et al,[9] and replications are awaiting. Remarkably, few studies have tested the predictions of the operant conditioning paradigm in patients with chronic pain. Romano et al. performed a sophisticated and complex sequential analysis of chronic pain patients' behaviors and spouse responses and showed that spouse solicitous behaviors were significantly more likely to precede and follow nonverbal pain behaviors, and this occurred more often than in control couples. These interactions also predicted patients' level of disability.[85,91,92] More recent studies have expanded operant conditioning formulations of patient–spouse interactions with interpersonal processes of intimacy, taking into account emotional content and validation of spouse responses.[17]

A second form of operant learning is when a particular behavior leads to the reduction of an aversive outcome, rather than to the occurrence of a rewarding outcome. Individuals may limit activity, display guarding or protective behaviors, or take analgesics because of anticipated nociceptive stimuli. Fordyce provides several illustrations of how various pain behaviors function as avoidance behaviors,[37,39] but experimental studies have been scarce. Avoidance behavior once acquired is notoriously persistent, and this has challenged the classic operant learning theory. When the aversive outcome is successfully avoided, no reinforcement is experienced anymore and rapid extinction should follow. One account is based on the opponent process theory,[54] predicting that the offset of an affective process of 1 valence brings about the onset of a complimentary affective response of the opposite valence. Avoidance of nociceptive input creates a relief that is intrinsically rewarding, which maintains the avoidance response.[52] Various alternative explanations have been formulated since, including those based on expectancy learning,[65] occasion setting[25] and action tendencies.[6] Finally, a bidirectional association between avoidance and threat has been proposed where one's own avoidance behavior is used as a source of information to derive danger, for example: "I am avoiding, therefore there must be danger."[3] Remarkably, and despite the various theoretical approaches and its clinical relevance, avoidance learning has received little scientific attention in the pain research field so far.[109]

3.1. Extinction

Whenever the reinforcement of a previously reinforced pain behavior is withheld and a second noncompatible behavior is shaped and successively reinforced, a decline in the rate of the previous behavior will be observed, which is called extinction (**Fig. 1F**). In his book "*Behavioral methods for chronic pain and illness*," Fordyce lays out a sophisticated behavioral technology for conducting a proper analysis of the behavior of individuals with chronic pain.[37,66] Fordyce also provides the key principles of contingency management programs for the extinction of dysfunctional pain behaviors, and to shape or reinforce functional healthy behaviors. Since then, his methods have been applied in most chronic pain management programs worldwide,[37] and with moderate to good effect sizes.[41,45]

3.2. Future directions

Although the operant conditioning model has significantly shaped the clinical management of chronic pain, there is remarkable little experimental research testing its basic assumptions.[41] Many questions deserve further interrogation, of which some are selected here. (1) What is the range of behaviors that can be modulated by operant conditioning? For example, an interesting series of studies by Hölz et al. suggest that increases or decreases of pain perception can serve as intrinsic reinforcers for short-term sensitization and habituation to tonic heat stimuli,[5,46] again suggesting a dynamic interplay between associative and nonassociative processes. (2) The learning processes that we have described so far do not occur in isolation, and a yet unanswered question is how operant conditioning interacts with Pavlovian conditioning? First, behavioral responses have (proprioceptive) stimulus properties that can act as CSs eliciting pain-related fear responses.[71] Conversely, Pavlovian-conditioned stimuli can influence instrumental responding.[100] CSs may increase/decrease instrumental behavior that associated a similar/dissimilar outcome. For example, the presence of a cue associated with a rewarding stimulus may strengthen nonpain health behavior that is being positively reinforced. This is a novel area that merits further scrutiny, and the findings are likely to contribute to the refinement of operant treatments for individuals with chronic pain.[66] (3) Although there are established ways of measuring pain behaviors, reliable and valid methods for the assessment of avoidance (and more subtle safety seeking) behaviors are currently lacking.[101,110] (4) Knowledge between potential cues and pain can be acquired indirectly, through observation and verbal information. The mere observation of another person in pain can be sufficient to install fearful responses of that particular stimulus.[42] Besides observation, verbally transmitted information can hold semantically negative information that may yield relevant conceptual knowledge about the patterns of events in the environment. For example, avoidance of activity may increase by the learning of rules (eg, "lifting weights may cause back injury"), without actually experiencing the suggested associations between these actions and their outcomes.[23] For example, the social perceptions that rest and inactivity are the best treatment for low back pain may serve to further reinforce rest and inactivity in the patient.[13,47]

4. Conclusions

Reiterating Rescorla[87] and others, conditioning is not just the simple process by which the individual inevitably forms associations between any 2 events, or a behavior and an event that happen to co-occur. Rather, conditioning is an active form of learning during which information about logical, meaningful, and perceptual relations among events is continuously sought. Insight in such patterns of relations is essential to allow the individual to form a sophisticated representation of the internal and external environment. Understanding the different ways events in the environment produce pain-related behavior changes, their mutual interactions, and the motivational context in which they occur is likely to be critical in understanding how common acute pain episodes may transform into disabling chronic pain states. This review is just scratching the surface of a vast but rich area of complex mechanisms that underlie conditioning in the area of pain, and promising biobehavioral research lies ahead of us. Evidently, the clinical application of these modern insights to the prevention and management of chronic pain has just begun.

Conflict of interest statement

The author declares no conflict of interest.

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