Current Pain and Headache Reports (2019) 23: 19
https://doi.org/10.1007/s11916-019-0766-0

PSYCHOLOGICAL AND BEHAVIORAL ASPECTS OF HEADACHE AND PAIN (D. BUSE, SECTION EDITOR)

Pavlov's Pain: the Effect of Classical Conditioning on Pain Perception and its Clinical Implications

Libo Zhang [1,2] · Xuejing Lu [1,2] · Yanzhi Bi [1,2] · Li Hu [1,2,3]

Published online: 5 March 2019

Abstract

Purpose of Review It has been known for decades that classical conditioning influences pain perception. However, the precise relationship between conditioning and pain remains unclear. In addition, the clinical implications of their relationship are vastly underappreciated. Thus, we aim to (a) examine how conditioning increases or decreases pain sensitivity, (b) assess how conditioning contributes to the development and maintenance of chronic pain, and (c) explore strategies to utilize conditioning to optimize pain treatment.

Recent Findings We first review studies regarding how classical conditioning alters pain perception with an emphasis on two phenomena where conditioning increases pain sensitivity (i.e., conditioned hyperalgesia) or decreases it (i.e., conditioned hypoalgesia). Specifically, we critically examine empirical studies about conditioned hyperalgesia and conditioned hypoalgesia, explore reasons why conditioning leads to these two seemingly opposite phenomena, and discuss the neural mechanisms behind them. We then highlight how conditioning contributes to the development and maintenance of chronic pain, and present neuroscientific evidence for maladaptive aversive conditioning in chronic pain patients. Moreover, we propose a framework for understanding how to exploit conditioning to optimize pain treatment, including minimizing conditioned hyperalgesia, maximizing conditioned hypoalgesia, and eliminating excessive fear and overgeneralization in chronic pain.

Summary Classical conditioning profoundly modulates the experience of pain and affects the development and maintenance of chronic pain. The relationship between them has far-reaching clinical implications in pain treatment. Further investigations should tackle crucial issues in previous studies, including the complex relationship between conditioning and explicit expectation, and a lack of relevant clinical studies. Resolving these issues, future research would advance our understanding of the nature of pain, help relieve the suffering of patients, and thus contribute to promoting human flourishing.

Keywords Classical conditioning · Conditioned hyperalgesia · Conditioned hypoalgesia · Chronic pain · Clinical implications

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage [1], whose biological functions are to identify possible threats of bodily harm, avoid tissue damage, and promote recovery from actual body damage [2]. These functions rest upon individual's learning ability. For example, avoiding future tissue damage presupposes the knowledge of what caused pain in the past. Furthermore, the role of learning in pain chronification is getting increasing attention in the pain society, and some researchers claimed that chronic pain is a consequence of the inability to extinguish the memory trace of pain [3, 4]. Therefore, a thorough understanding of the nature and treatment of pain warrants a

This article is part of the Topical Collection on *Psychological and Behavioral Aspects of Headache and Pain*

✉ Xuejing Lu
luxj@psych.ac.cn

✉ Li Hu
huli@psych.ac.cn

1 CAS Key Laboratory of Mental Health, Institute of Psychology Chinese Academy of Sciences, Beijing, China

2 Department of Psychology, University of Chinese Academy of Sciences, Beijing, China

3 Department of Pain Management, The State Key Clinical Specialty in Pain Medicine, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

comprehensive appreciation of the interaction between learning and pain.

As a basic form of learning, classical conditioning, or Pavlovian conditioning, which establishes associations between two events in the most general terms [5], has been linked to changes of pain sensitivity (quantified as pain threshold, pain tolerance, or pain ratings to nociceptive stimuli) in many studies [6••, 7•, 8, 9]. In a typical classical conditioning procedure, a neutral stimulus (conditioned stimulus, CS) is repeatedly paired with a potent stimulus (unconditioned stimulus, US) that evokes a biologically meaningful response (unconditioned response, UR). After several times of learning, the CS can, by itself, elicit a response (conditioned response, CR) related to the UR. Importantly, some researchers and clinicians believe that pain is a classically conditioned response [10, 11], and conditioning plays a significant role in the development and maintenance of chronic pain [3, 11, 12]. However, the precise relationship between conditioning and pain remains largely unclear, and clinical implications of their relationship are vastly underappreciated [13].

In this article, we review relevant studies that assessed the relationship between classical conditioning and pain (see Fig. 1). Specifically, we first discuss two phenomena caused by conditioning: one is that pain sensitivity is increased, namely conditioned hyperalgesia; the other is that pain sensitivity is decreased, namely conditioned hypoalgesia. We then provide evidence on how conditioning contributes to the development and maintenance of chronic pain, and discuss possible clinical implications of the relationship between classical conditioning and pain. Finally, we point out crucial issues that need to be addressed in the future.

Conditioned Hyperalgesia and Conditioned Hypoalgesia

Conditioned hyperalgesia has been defined as the phenomenon that classical conditioning increases one's pain sensitivity [8, 14]. In contrast, conditioned hypoalgesia refers to the phenomenon that pain sensitivity is reduced after classical conditioning [8, 15]. However, both definitions are oversimplified to some extent and may cause confusions with other concepts, especially conditioned nocebo hyperalgesia and conditioned placebo hypoalgesia.

The difference between conditioned hypoalgesia and conditioned placebo hypoalgesia seems to lie in the cause of hypoalgesia. The former describes situations where classical conditioning itself modulates pain sensitivity, and the latter refers to the placebo effect induced by a conditioned placebo paradigm [16]. In the paradigm, verbal information about the link between the CS and the US is often, if not always, disclosed to the subjects, which indicates that subjects hold explicit expectations about the effect of conditioning [17–22]. This difference may appear to be a good candidate to distinguish conditioned hypoalgesia and conditioned placebo hypoalgesia. However, classical conditioning and expectation have an exceedingly complicated relationship, and they cannot be easily distinguished in practice (see "Future Directions"). Therefore, we adopt a broader definition of conditioned hypoalgesia and include all studies that make use of the classical conditioning paradigm to induce hypoalgesia. The same logic also applies to conditioned hyperalgesia and conditioned nocebo hyperalgesia. In other words, we define in this article conditioned hyperalgesia/hypoalgesia as the phenomenon that individuals feel more/less pain to the same nociceptive stimulus after classical conditioning (see Fig. 2), regardless of whether verbal information or explicit expectation is involved or not.

Empirical Studies on Conditioned Hyperalgesia and Conditioned Hypoalgesia

Conditioned Hyperalgesia

The effect of conditioned hyperalgesia has been well-established in many studies [7•, 23–26]. For example, Madden et al. [25] investigated whether classical conditioning could decrease pain threshold in healthy adults using a differential conditioning paradigm (see Fig. 2), in which one CS (CS+) is paired with the US (e.g., a painful laser stimulus), and another CS (CS−) is not paired with any US or paired with a distinct US (e.g., a warm laser stimulus). The study mainly consisted of two phases: the conditioning phase and the test phase. In the conditioning phase, the CS+ and the CS−, two vibrotactile stimuli delivered at different locations on the back, were paired with a painful laser stimulus and a warm laser stimulus, respectively. In the test phase, both the CS+ and the CS− were followed by painful laser stimuli of the same intensity. It was found that the CS+, but not the CS−, lowered the pain threshold in the test phase, indicating that conditioned hyperalgesia can be established using classical conditioning. The same conditioned hyperalgesic effect was also observed in studies where different types of US were adopted, such as electrical shocks [26] and contact heat [24]. Intriguingly, conditioned hyperalgesia occurs even when the CS is presented implicitly, namely, the duration of the CS is very short, for example, tens of milliseconds. Harvie et al. [23] altered the CS duration to examine whether conditioned hyperalgesia was driven by the expectation about the association between the CS and the US. It turned out that the CS duration did not influence the magnitude of conditioned hyperalgesia, suggesting an implicit conditioned hyperalgesia. With the help of visual masking techniques, Egorova et al. [27], Jensen et al. [24], and Egorova, Park, and Kong [28] offered further evidence for the existence of implicit conditioned hyperalgesia.

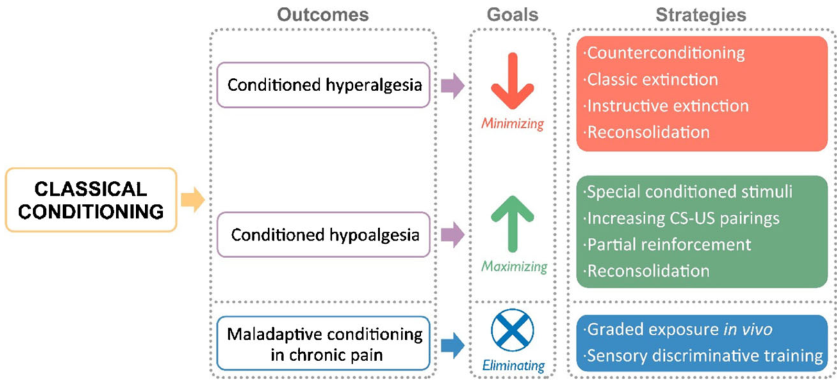

Fig. 1 Schematic diagram indicating how classical conditioning affects pain and its clinical implications. Classical conditioning may increase (conditioned hyperalgesia) or decrease (conditioned hypoalgesia) pain sensitivity. Classical conditioning could also result in maladaptive conditioning, such as excessive fear and overgeneralization, which contributes to the development and maintenance of chronic pain. To effectively reduce/eliminate unwanted pain, we could adopt some promising strategies, which aim to minimize conditioned hyperalgesia, maximize conditioned hypoalgesia, and eliminate excessive conditioned fear and overgeneralization

A few studies, however, failed to establish conditioned hyperalgesia [29–32]. It should be noted that all these studies relied on conditioning exclusively, and that verbal information about the association between the CS and the US was not available. It is therefore plausible that, without verbal information, conditioning itself results in a less strong or undetected conditioned hyperalgesia effect, as suggested in Reicherts et al. [33].

Conditioned Hypoalgesia

The effect of conditioned hypoalgesia has been well-documented in a large number of studies [17, 18, 20, 24, 33–36]. For example, Jensen et al. [24] used male face pictures as the CS, and contact thermal pain stimuli as the US, and found that subjects perceived the same thermal stimulus as less painful when it was preceded by a face associated with a low pain stimulus rather than a new face that was never paired with any US. Interestingly, they also found the same hypoalgesic effect even when the CS was presented for 12 ms and followed by a visual mask, indicating the existence of implicit conditioned hypoalgesia. Moreover, conditioned hypoalgesia has been successfully established with different types of the US, for example, painful laser stimuli [37, 38] and painful electrical stimuli [34, 35].

However, several recent studies failed to establish conditioned hypoalgesia [39–41]. Two reasons might explain these failures. First, some of these studies introduced a negative expectation about the effect of the treatment by telling subjects that they might not [40] or would not [41] receive an analgesic drug or cream, and the negative expectation about the treatment efficacy may dampen the effect of classical conditioning, which in turn leads to the failure of establishing conditioned hypoalgesia. Second, the number of CS-US pairings in the conditioning phase was too small to induce a detectable conditioned hypoalgesia effect in some studies, for example, 2 pairings in Flaten et al. [40] and 12 pairings in Rhudy et al. [41].

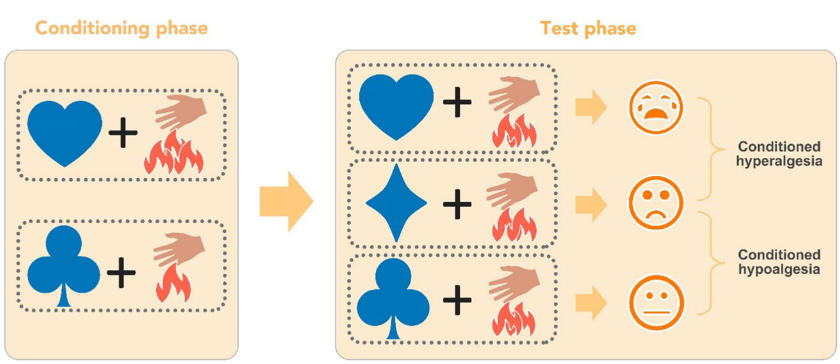

Fig. 2 Conditioned hyperalgesia and conditioned hypoalgesia. The differential conditioning paradigm is widely used to investigate how conditioning affects pain. The paradigm consists of a conditioning phase and a test phase. In the conditioning phase, one CS (e.g., a heart icon) is paired with a US (e.g., painful heat), and another CS (e.g., a club icon) is paired with a distinct US (e.g., less painful or non-painful heat). In the test phase, both CS and a new stimulus (e.g., a diamond icon) are followed by the same test stimulus. Conditioned hyperalgesia occurs if the heart icon leads to a higher pain compared to the diamond icon, and conditioned hypoalgesia occurs if the club icon leads to a lower pain compared to the diamond icon

Why Conditioned Hyperalgesia and Conditioned Hypoalgesia?

Existing studies support the existence of two seemly paradoxical phenomena: classical conditioning decreases AND increases pain sensitivity. This paradox suggests the existence of extra variables that could modulate the relationship between classical conditioning and pain sensitivity. The nature of classical conditioning indicates that potential modulating variables may include properties of the US [14, 42] and the CS [8].

Relative stimulus intensity, the difference of stimulus intensity between a target US and a control US, is one of the most obvious properties of the US that could influence the effect of conditioning. In the differential conditioning paradigm, the target US can be defined as the US paired with the CS+; the control US can be defined as the US paired with the CS−. In this case, positive/negative relative stimulus intensity means that the intensity of the target US is higher/lower than that of the control US, which would result in conditioned hyperalgesia/conditioned hypoalgesia. The importance of relative stimulus intensity has been confirmed in many studies [18, 24, 27, 28, 43, 44]. For example, Jensen et al. [24] found that, as compared with new faces that were not paired with any US, male faces associated with contact heat stimuli of positive relative intensity led to conditioned hyperalgesia, whereas male faces coupled with heat stimuli of negative relative intensity generated conditioned hypoalgesia.

In addition to relative stimulus intensity, emotional valence of the US could also modulate the relationship between conditioning and pain sensitivity: generally speaking, positive emotions decrease pain and negative emotions increase pain [45]. It should be noted that different negative emotions may lead to different outcomes. For example, Rhudy and Meagher [42] demonstrated that conditioned fear decreased pain sensitivity, whereas conditioned anxiety increased it, which was supported by multiple lines of evidence [46–49].

Apart from the properties of the US, the type of the CS could be another variable modulating the relationship between conditioning and pain sensitivity. Miguez et al. [8] reviewed studies about conditioned hyperalgesia and conditioned hypoalgesia, and concluded that olfactory and gustatory CS produced conditioned hyperalgesia, and that visual, auditory, and contextual CS evoked conditioned hypoalgesia. It is important to note that, if paired with a US of positive relative intensity, audiovisual CS are still able to induce conditioned hyperalgesia [7•], indicating how different modulating variables interact with each other to determine the overall conditioning effect.

In brief, certain properties of the US and the CS are effective in modulating the relationship between classical conditioning and pain sensitivity. However, the existence and the effectiveness of other modulating variables, and the complex interplay between those modulators are not thoroughly studied. Both questions call for further investigations.

Neural Mechanisms of Conditioned Hyperalgesia and Conditioned Hypoalgesia

Conditioned Hyperalgesia

Conditioned hyperalgesia is probably mediated by anxiety [42], which is supported by accumulating evidence from neurochemical and neuroimaging studies. On the one hand, the contribution of cholecystokinin (CCK), the neurochemical basis of anxiety [50], to the modulation of verbally-induced nocebo effects has been well documented [51, 52], even though the direct role of CCK in conditioned hyperalgesia has rarely been tested. Since verbally-induced nocebo [50] and conditioned hyperalgesia [42] are both dependent on the mediation of anxiety, it would be reasonable to hypothesize that CCK is also involved in conditioned hyperalgesia.

On the other hand, neuroimaging studies have demonstrated that the conditioned anxiety engenders activation of the brain regions that contribute substantially to the development of conditioned hyperalgesia. Amygdala and insula, two important nuclei subserving the processing of anxiety [53, 54], were more activated when thermal pain stimuli were delivered following the CS+ rather than the CS− [55]. The functional connectivity between these two regions was also found to be elevated in conditioned hyperalgesia [56]. Additionally, hippocampus, a key area for the formation and expression of the conditioned anxiety triggered by the CS [57, 58], was more activated to the presentation of the CS+ rather than the CS− in the test phase [30, 48, 55, 56, 59].

Conditioned Hypoalgesia

Classical conditioning probably decreases pain sensitivity by modulating subject's psychological states, such as expectation and emotion [60], which in turn activate the descending pain inhibitory system and generates hypoalgesic effects by inhibiting the ascending nociceptive signals [61]. This notion is supported by many neurochemical and neuroimaging studies. At the neurochemical level, the descending pain inhibitory system could be activated or deactivated by multiple neurotransmitters, including endogenous opioid, endocannabinoid, gamma-Aminobutyric acid (GABA), and glutamate [61, 62]. Conditioned hypoalgesia could be attenuated or even reversed by the administration of antagonists or agonists of these neurotransmitters [34, 47, 63–66]. For example, Flor et al. [34] showed that conditioned hypoalgesia was reversed if naloxone, an antagonist of endogenous opioid, was injected, but remained if physiological saline was injected. Conditioned hypoalgesia could also be attenuated by the administration of diazepam [67], benzodiazepine [68], or midazolam [69], all of which could enhance the effect of GABA, an inhibitory neurotransmitter.

Neuroimaging studies have provided further evidence to support the role of the descending inhibition system in conditioned hypoalgesia. In the descending inhibition system, periaqueductal gray (PAG) receives inputs from higher brain areas and projects to the spinal dorsal horn via rostral ventromedial medulla (RVM) [70, 71]. Using the functional magnetic resonance imaging (fMRI) technique, Bingel et al. [72] observed a significant activation of PAG, but not of RVM, in conditioned hypoalgesia. The small size of RVM and the limited spatial resolution of fMRI probably explain why the activation of RVM was absent. Using special techniques to increase the spatial resolution, Eippert et al. [73] successfully found that both PAG and RVM were activated in conditioned hypoalgesia.

As explained earlier, the effect of conditioned hypoalgesia could be modulated by many psychological variables, such as expectation and emotion. Importantly, brain regions related to these psychological variables (e.g., hippocampus, dorsolateral prefrontal cortex (dlPFC), ventromedial prefrontal cortex, rostral anterior cingulate cortex, and amygdala) have been demonstrated to be involved in conditioned hypoalgesia [37, 55, 72, 74, 75]. For example, delivering low-frequency repetitive transcranial magnetic stimulation to disrupt the function of dlPFC, an area implicated in expectation and anticipation [37, 74, 75], Krummenacher et al. [74] successfully blocked conditioned hypoalgesia. In addition, many studies found that lesions of amygdala, a crucial nuclei for emotional processing [57], resulted in a diminution or even an elimination of conditioned hypoalgesia [76–78].

Classical Conditioning and Chronic Pain

Classical conditioning influences not only acute pain but also chronic pain, which persists even when tissue damage has been recovered [79]. In this section, we first delineate influential theoretical models regarding how conditioning contributes to the development and maintenance of chronic pain, and then discuss neuroscientific evidence for altered pain-related conditioning in chronic pain patients.

Theoretical Models of Conditioning in Chronic Pain

Gentry and Bernal [80] were the first to expound classical conditioning's role in the development of chronic pain. They suggested that innocuous stimuli (CS), such as certain body positions, might be paired with nociceptive stimuli (US), and that after conditioning these innocuous stimuli could elicit conditioned responses resembling the UR, such as fear, sympathetic activation, and increased muscle tension. This viewpoint is supported by the findings that patients suffering from chronic pain showed larger conditioned muscle tension responses than healthy subjects [81, 82].

The importance of classical conditioning in pain chronification is also emphasized in the fear-avoidance model [83]. The model states that individuals would respond to pain with two different strategies: confrontation or avoidance [12, 84]. If the confrontation strategy is adopted, no excessive pain-related fear would be experienced and pain would cease after the healing of injury. In contrast, if the avoidance strategy (i.e., catastrophizing pain) is adopted, pain-related fear would evolve, which in turn leads to disability, disuse, hypervigilance, and misinterpretation of bodily sensations. These overreactions to pain would further increase fear, thus forming a vicious circle of fear and avoidance, which contributes significantly to the elevation of pain sensitivity and persistence of excruciating pain. This model is supported by abundant findings that pain catastrophizing and fear of pain were strong predictors of chronic pain [85–88].

Gentry and Bernal's [80] explication of pain chronification and the fear-avoidance model [83] focus on how pain-related psychological states and physiological activations are classically conditioned. However, they rely on the assumption that pain is the consequence of fear and muscle tension, and do not regard pain as the target of conditioning. Holding the view that pain per se is an immediate conditioned response [11], the imprecision hypothesis claims that the imprecise encoding of pain-related stimuli or events leads to overgeneralization, which contributes to the development and maintenance of chronic pain. Specifically, if overgeneralization happens to patients who suffer from excruciating pain, neutral stimuli not associated with the US but resembling the CS would exacerbate pain, such that the adaptive and protective process becomes maladaptive and dysfunctional. Indeed, a recent meta-analysis study found that patients with chronic pain had an impaired discrimination ability [89], indicating the prevalence of overgeneralization in chronic pain patients.

In summary, multiple theoretical models posit the importance of conditioning—maladaptive conditioning such as excessive conditioned fear and overgeneralization in particular—in the development and maintenance of chronic pain.

Neural Mechanisms of Maladaptive Conditioning in Chronic Pain

Neural mechanisms of maladaptive conditioning in chronic pain are not well understood. However, there are a handful of interesting and inspiring findings. Using a typical differential conditioning paradigm, Schneider, Palomba, and Flor [82] found that chronic low back pain patients did not exhibit a significant CS+ and CS− differentiation of contingent negative variation (CNV) in the last several trials of the conditioning phase. The CNV is a typical cortical measure of the association between the CS and the US [90], and thus the insignificant difference of CNV indicated an impaired conditioning ability of patients at the cortical level. In addition, compared to healthy adults, patients with irritable bowel syndrome (IBS) had altered activity in brain regions associated with fear, hypervigilance, and threat assessment in the conditioning phase, such as ventrolateral prefrontal cortex, posterior cingulate cortex, amygdala [91], and subregions of cerebellum [92], supporting the role of excessive fear in the development of chronic pain for IBS patients.

Clinical Implications

Since pain, especially chronic pain, is a main source of human suffering and ranks among the most burdensome non-fatal diseases in the world [93], eradicating unnecessary pain is a major goal for scientists and clinicians in the whole pain society. To achieve this, minimizing conditioned hyperalgesia and maximizing conditioned hypoalgesia are two desirable goals, since classical conditioning may increase or decrease pain under certain circumstances. Moreover, the theoretical models of pain chronification we described earlier offer insights into effective chronic pain treatment through eliminating excessive conditioned fear and overgeneralization (for a summary, see “Goals” and “Strategies” in Fig. 1).

Minimizing Conditioned Hyperalgesia

Minimizing conditioned hyperalgesia can be achieved by making use of effective techniques to combat the adverse effect of associative learning. Unfortunately, relevant studies discussing how to erase conditioned hyperalgesia are still lacking, and most studies focus on developing strategies for eliminating conditioned fear. Therefore, we mainly introduce how conditioned fear can be eradicated, hoping that these studies could stimulate further investigations into erasing conditioned hyperalgesia.

Conditioned fear, which develops because of the continuous CS-US pairings, would be diminished by counterconditioning and classical extinction, as both techniques aim to disrupt the link between the CS and the US. The counterconditioning technique weakens conditioned fear by pairing the same CS with an appetitive US after the initial conditioning [94]. Meulders et al. [95] investigated whether counterconditioning was able to reduce conditioned fear using a voluntary joystick movement paradigm [96], in which moving a joystick in different directions (CS) was associated with different outcomes (US). They first paired one direction of the joystick with a painful electrical shock, and then paired it with a US representing monetary rewards. This procedure turned out to successfully decrease conditioned fear [95].

In contrast, the extinction technique intends to reduce or eliminate the effect of conditioning by no longer pairing the CS with any US once conditioning has been established [97]. Several studies found that visceral pain-related fear was reduced, though not eliminated altogether, after subjects underwent classical extinction procedures [98–100]. Importantly, Meulders et al. [95] compared the effects of counterconditioning and classical extinction on attenuating movement-related fear, and found that they produced comparable effects. Recently, Maeda et al. [101] optimized the effect of extinction by combining it with the provision of verbal information about the detailed procedure of extinction (i.e., the CS would not be followed with the US any more), and found that the effect of this “instructive extinction” was significantly better than that of classical extinction.

Although extinction has been proved to be effective, it is noteworthy that extinction only inhibits the retrieval of relevant memories, and that it does not erase the memories themselves [97, 102]. For this reason, the memories would re-emerge if a large amount of time has passed (spontaneous recovery), the US is delivered unexpectedly (reinstatement), or the CS is presented in a context different from that of extinction (renewal) [103]. Fortunately, these issues could be resolved by methods based on memory reconsolidation, an active process necessary for long-term memories to be restabilized after being activated and destabilized [104, 105]. According to the reconsolidation hypothesis, memories can be literally erased by intervening the reconsolidation process, and thus will not re-emerge any more [103, 106]. In fact, the effect of reconsolidation-inspired techniques has been validated in different species (e.g., rats, mice, and humans) and research domains (e.g., fear conditioning, declarative memory, and drug craving) [103, 107–112]. For clinical applications, disruption of reconsolidation in humans can be achieved using drugs such as Propranolol and Ketamine, and behavioral procedures such as retrieval-extinction [113].

In spite of being relatively scarce, some studies have attempted to extinguish conditioned hyperalgesia [27, 28, 43, 114, 115], concluding that the effect of conditioned hyperalgesia was difficult to reverse using classical extinction [116•]. However, the failure of extinction might be explained by two reasons. First, no independent extinction procedure was included in most studies [21, 43, 114, 115]. A typical procedure used in previous studies was as follows: subjects were classically conditioned, and went through a “test/extinction” phase, where subjects rated how much pain they felt when a pain stimulus was delivered following the CS. If conditioned hyperalgesia continues in the entire “test/extinction” phase, it was claimed to be immune to extinction. The purpose of the “test/extinction” phase was thus arguably twofold: (1) to test whether subjects were successfully conditioned and (2) to examine the effect of extinction. In contrast to the standard procedure of extinction where no US is paired with the CS [97], the operation that pain stimuli (US) were delivered following the CS in the "test/extinction" phase would weaken the extinction effect. Second, explicit expectation, typically induced by the verbal information about the efficacy of the treatment, was involved in many studies [27, 115]. The failure of extinction thus might be either due to the strong expectation subjects held about the conditioning effect, or due to the intrinsic characteristic of conditioned hyperalgesia. To better understand the extinction of conditioned hyperalgesia, it would be important to exclude the confounding of explicit expectation.

Furthermore, even if extinction is indeed unable to reduce conditioned hyperalgesia, the efficacy of other methods is worthwhile to evaluate. Some researchers have suggested that methods such as latent inhibition and overshadowing, though rarely examined, would be effective in reversing conditioned hyperalgesia [116•]. Latent inhibition, sometimes termed as the CS-preexposure effect, impairs learning about the relationship between the CS and the US by pre-exposing subjects to the CS before conditioning [117]. Overshadowing refers to the phenomenon that when two stimuli of different saliency are paired simultaneously with a US, the conditioned response to the less salient stimulus will be weakened. Please note that empirical studies have already demonstrated that latent inhibition [118, 119] and overshadowing [120–122] can block the nocebo effect of nausea. To minimize conditioned hyperalgesia, future studies are required to directly test the efficacy of these alternative methods.

Maximizing Conditioned Hypoalgesia

Conditioned hypoalgesia is a longed-for outcome in clinical applications. Therefore, maximizing conditioned hypoalgesia, that is, keeping the effect as strong as possible and as long as possible, is highly needed. To obtain a greater conditioned hypoalgesia effect, the conditioning paradigm should be optimized by, for example, choosing an appropriate CS type and increasing the number of CS-US pairings. The importance of CS type is supported by Valentini et al. [38]. They used happy, neutral, and painful faces as the CS, and painful laser stimuli as the US, and found that happy faces led to a greater conditioned hypoalgesia effect compared to other two types of CS. The role of the number of CS-US pairings is confirmed by Colloca et al. [43] and Schafer et al. [36], who showed that a larger number of trials gave rise to a larger conditioned hypoalgesia effect.

Apart from generating a greater effect, an optimized conditioned paradigm is also able to induce a persistent conditioned hypoalgesia. For example, Egorova et al. [28] found that using human faces as the CS rather than abstract images and pseudowords established a conditioned hypoalgesia withstanding extinction. Additionally, partial reinforcement schedules, in which the CS is not always paired with the US in the conditioning phase, i.e., $P(\text{US}|\text{CS}) < 1$ [123], were also found to be effective in preserving conditioned hypoalgesia [20].

Moreover, reconsolidation-inspired techniques are also promising in keeping conditioned hypoalgesia as persistent as possible. As mentioned in the previous section, the reconsolidation hypothesis asserts that long-term memories are prone to modification after being retrieved. Importantly, such modification includes enhancing existent memories. In fact, human studies have proved that an administration of a mild stressor or glucose after retrieval of old memory strengthened declarative memory [124, 125]. Being scarce currently, further studies may attempt to examine the efficacy of reconsolidation-inspired techniques in extending conditioned hypoalgesia in the future.

Eliminating Excessive Fear and Overgeneralization

Since excessive conditioned fear and overgeneralization are supposedly responsible for the transition from acute pain to chronic pain, eliminating them are two important goals in developing effective treatments of chronic pain.

Inspired by the fear-avoidance model, graded exposure in vivo (GEXP) is one of the promising treatments focusing on eliminating excessive conditioned fear. GEXP consists of three steps: cognitive-behavioral assessment, education, and exposure in vivo [126]. Cognitive-behavioral assessment determines the idiosyncratic aspects of pain-related fear for each patient using questionnaires, interviews, and behavioral tests, which help establish graded hierarchies of pain-related fear. In the step of education, the therapist explains the fear-avoidance model to the patient and corrects misinterpretations and misconceptions the patient has about chronic pain. In the final step, the patient is exposed to fearful events in a hierarchical way and encouraged to perform fearful activities that were intentionally avoided.

The efficacy of GEXP has been attested across a variety of chronic pain, such as chronic low back pain [127–132], complex regional pain syndrome type I [133], work-related upper extremity pain [134], and spinal pain [135]. It successfully reduced pain-related fear, catastrophizing, and functional disability [127, 129–135], and the effects persisted up to 6 months after treatment [132, 134]. However, most studies adopted single-case designs with a limited number of subjects. Further studies using more rigorous designs (e.g., randomized controlled trials) and a larger sample size are highly needed to ascertain the efficacy of GEXP in reducing chronic pain.

Targeted on eliminating overgeneralization, sensory discrimination training has received much attention. Since overgeneralization arises due to the unwanted ability of stimuli resembling the CS to elicit the CR, it might be reversed by sensory discrimination training, which improves patients' discriminative ability by training them to distinguish different sensory inputs (e.g., tactile stimuli delivered at different locations) that may serve as potential CS. In addition, sensory discrimination training could also undo cortical reorganization, the structural and functional alterations in the representational maps of sensory and motor information in the brain resulting from chronic pain [136–138]. This technique has been confirmed to alleviate pain in phantom limb pain [139, 140], chronic low back pain [141–143], and complex regional pain syndrome type I [144–147]. It is noteworthy that most existing studies trained patients to distinguish tactile stimuli. Some interesting questions for the future thus would be: Would it be still effective if training is focused on other sensory modalities (e.g., visual, auditory, or even painful stimulation)? Will it be better to combine other sensory information (e.g., visual feedback) with tactile stimulation in training?

Future Directions

Classical conditioning can influence pain perception by altering pain sensitivity and contributing to the development and maintenance of chronic pain, and has far-reaching clinical implications in pain treatment. However, there are two major unsolved issues awaiting future investigation.

One is that the complex relationship between classical conditioning and explicit expectation poses a serious obstacle for attempts to elucidate the psychological mechanisms of conditioned hyperalgesia and hypoalgesia. Many existing studies combine conditioning and verbal information to induce a hyperalgesic or hypoalgesic effect [17, 18, 59, 148]. As a result, any success or failure in establishing conditioned hyperalgesia or hypoalgesia might be attributed to either or both of them. Some promising strategies have been proposed to disentangle classical conditioning from explicit expectation, but most of them are imperfect solutions.

For example, implicit conditioning, in which the CS is presented for only tens of milliseconds and is followed by a visual mask [24, 27, 28, 44], has been suggested to be able to rule out the contribution of expectation [6••]. However, implicitness is not identical to unconsciousness [149–151], and thus implicit conditioning does not necessarily exclude the involvement of conscious expectation. The open-label design, where subjects are informed of the placebo or nocebo manipulations after the conditioning phase [19, 36], is another promising approach to exclude the confounding influence of expectation. Nevertheless, this design does not preclude the involvement of expectation, but intends to exclude the influence of it ex post on the basis of the not easily testable assumption that verbal information makes subjects unlearn the association between the CS and the US. Studies about subjects with minimal cognitive abilities such as invertebrates [152], decerebrate humans [153], and isolated spinal cords [154] also offer possibilities to test the unique contribution of conditioning. The problem with this strategy is whether pain or nociception is still an appropriate descriptor for these subjects and to what extent results from them and humans are comparable. In summary, the confounding influence of expectation in conditioned hyperalgesia and conditioned hypoalgesia seems intractable at present, and it necessitates further investigations to help improve existing strategies and develop novel strategies.

The other important issue is that the number of studies working on chronic pain patients is quite limited compared to those recruiting healthy subjects. Even though plenty of theoretical and empirical evidence has suggested a bright future of exploiting conditioning in treating chronic pain, a lack of relevant clinical studies hinders a thorough appreciation of the clinical value of conditioning. Two further issues should also be considered for future clinical studies. First, longitudinal studies are in need to track the development, maintenance, and, if possible, recovery of chronic pain in the future. Different from the widely-used cross-sectional designs, which compare healthy subjects and patients at a given time point, longitudinal studies would be able to identify the causal role of conditioning in pain chronification and recovery. Second, since chronic pain is not a homogeneous disease, but one that can be further divided into many categories [155], whose etiology and treatments would be different, comparing the effects of conditioning in different categories of chronic pain will be highly informative and beneficial.

Conclusions

Classical conditioning has been demonstrated to profoundly modulate the experience of pain and partly shape pain's role in human health. This article provides a comprehensive review of the classical conditioning aspects of acute and chronic pain, and discusses extensively the prospects of utilizing conditioning in pain treatment. A systematic knowledge of conditioning's role in pain furthers our understanding of the nature of pain, helps relieve the suffering of patients, and thus contributes to promoting human flourishing.

Acknowledgments We thank Fengrui Zhang for his invaluable help with illustrating figures.

Funding Information This work was supported by the National Natural Science Foundation of China (No. 31671141, 31701000, 31822025), the Informatization Special Project of Chinese Academy of Sciences (No. XXH13506-306), and the Scientific Foundation Project of Institute of Psychology, Chinese Academy of Sciences (No. Y6CX021008, KLMH2018ZG02).

Compliance with Ethical Standards

Conflict of Interest Statement The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Loeser JD, Treede R-D. The Kyoto protocol of IASP basic pain terminology. Pain. 2008;137:473–7.
2. Tabor A, Thacker MA, Moseley GL, Körding KP. Pain: a statistical account. PLoS Comput Biol. 2017;13:e1005142.
3. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Prog Neurobiol. 2009;87:81–97.
4. Mazza S, Frot M, Rey AE. A comprehensive literature review of chronic pain and memory. Prog Neuro-Psychopharmacol Biol Psychiatry. 2018;87:183–92.
5. Rescorla RA. Pavlovian conditioning: it's not what you think it is. Am Psychol. 1988;43:151–60.
6.•• Bräscher A, Witthöft M, Becker S. The underestimated significance of conditioning in placebo hypoalgesia and nocebo hyperalgesia. Pain Res Manag. 2018;2018:1–8. **A highly relevant review that discussed how classical conditioning contributed to placebo hypoalgesia and nocebo hyperalgesia independently of explicit expectation.**
7.• Madden VJ, Harvie DS, Parker R, Jensen KB, Vlaeyen JWS, Moseley GL, et al. Can pain or hyperalgesia be a classically conditioned response in humans? A systematic review and meta-analysis. Pain Med. 2016;17:1094–111. **A very good systematic review showing that classical conditioning can augment pain perception.**
8. Miguez G, Laborda MA, Miller RR. Classical conditioning and pain: conditioned analgesia and hyperalgesia. Acta Psychol (Amst). 2014;145:10–20.
9. Turk DC, Fernandez E. Cognitive-behavioral management strategies for pain and suffering. Curr Pain Headache Rep. 1997;1:99–106.
10. Madden VJ, Moseley GL. Do clinicians think that pain can be a classically conditioned response to a non- noxious stimulus? Man Ther. 2016;22:165–73.
11. Moseley GL, Vlaeyen JWS. Beyond nociception: the imprecision hypothesis of chronic pain. Pain. 2015;156:35–8.
12. Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain. 2000;85:317–32.
13. Peerdeman KJ, van Laarhoven AIM, Keij SM, Vase L, Rovers MM, Peters ML, et al. Relieving patients' pain with expectation interventions: a meta-analysis. Pain. 2016;157:1179–91.
14. Jennings EM, Okine BN, Roche M, Finn DP. Stress-induced hyperalgesia. Prog Neurobiol. 2014;121:1–18.
15. Butler RK, Finn DP. Stress-induced analgesia. Prog Neurobiol. 2009;88:184–202.
16. Colloca L, Grillon C. Understanding placebo and nocebo responses for pain management. Curr Pain Headache Rep. 2014;18:419.
17. Colloca L, Benedetti F. How prior experience shapes placebo analgesia. Pain. 2006;124:126–33.
18. Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. Pain. 2008;136:211–8.
19. Wei H, Zhou L, Zhang H, Chen J, Lu X, Hu L. The influence of expectation on nondeceptive placebo and nocebo effects. Pain Res Manag. 2018;2018:8459429. https://doi.org/10.1155/2018/845942.
20. Yeung STA, Colagiuri B, Lovibond PF, Colloca L. Partial reinforcement, extinction, and placebo analgesia. Pain. 2014;155:1110–7.
21. Zhang H, Zhou L, Wei H, Lu X, Hu L. The sustained influence of prior experience induced by social observation on placebo and nocebo responses. J Pain Res. 2017;10:2769–80.
22. Zhou L, Wei H, Zhang H, Li X, Bo C, Wan L, et al. The influence of expectancy level and personal characteristics on placebo effects: psychological underpinnings. Front Psychiatry. 2019;10:20. https://doi.org/10.3389/fpsyt.2019.00020.
23. Harvie DS, Meulders A, Madden VJ, Hillier SL, Peto DK, Brinkworth R, et al. When touch predicts pain: predictive tactile cues modulate perceived intensity of painful stimulation independent of expectancy. Scand J Pain. 2016;11:11–8.
24. Jensen K, Kircher I, Odmalm S, Kaptchuk TJ, Ingvar M. Classical conditioning of analgesic and hyperalgesic pain responses without conscious awareness. Proc Natl Acad Sci. 2015;112:7863–7.
25. Madden VJ, Bellan V, Russek LN, Camfferman D, Vlaeyen JWS, Moseley GL. Pain by association? Experimental modulation of human pain thresholds using classical conditioning. J Pain. 2016;17:1105–15.
26. Williams AE, Rhudy JL. The influence of conditioned fear on human pain thresholds: does preparedness play a role? J Pain. 2007;8:598–606.
27. Egorova N, Park J, Orr SP, Kirsch I, Gollub RL, Kong J. Not seeing or feeling is still believing: conscious and non-conscious pain modulation after direct and observational learning. Sci Rep. 2015;5:16809.
28. Egorova N, Park J, Kong J. In the face of pain: the choice of visual cues in pain conditioning matters. Eur J Pain. 2017;21:1243–51.
29. Harvie DS, Sterling M, Smith AD. Do pain-associated contexts increase pain sensitivity? An investigation using virtual reality. Scand J Pain. 2018;18:525–32.
30. Icenhour A, Labrenz F, Ritter C, Theysohn N, Forsting M, Bingel U, et al. Learning by experience? Visceral pain-related neural and behavioral responses in a classical conditioning paradigm. Neurogastroenterol Motil. 2017;29:e13026.
31. Labrenz F, Icenhour A, Schlamann M, Forsting M, Bingel U, Elsenbruch S. From Pavlov to pain: how predictability affects the anticipation and processing of visceral pain in a fear conditioning paradigm. NeuroImage. 2016;130:104–14.
32. Madden VJ, Russek LN, Harvie DS, Vlaeyen JWS, Moseley GL. Classical conditioning fails to elicit allodynia in an experimental study with healthy humans. Pain Med. 2016;18:1314–25.
33. Reicherts P, Gerdes ABM, Pauli P, Wieser MJ. Psychological placebo and nocebo effects on pain rely on expectation and previous experience. J Pain. 2016;17:203–14.
34. Flor H, Birbaumer N, Schulz R, Grüsser SM, Mucha RF. Pavlovian conditioning of opioid and nonopioid pain inhibitory mechanisms in humans. Eur J Pain. 2002;6:395–402.
35. Flor H, Grosser SM. Conditioned stress-induced analgesia in humans. Eur J Pain. 1999;3:317–24.
36. Schafer SM, Colloca L, Wager TD. Conditioned placebo analgesia persists when subjects know they are receiving a placebo. J Pain. 2015;16:412–20.
37. Lui F, Colloca L, Duzzi D, Anchisi D, Benedetti F, Porro CA. Neural bases of conditioned placebo analgesia. Pain. 2010;151:816–24.

38. Valentini E, Martini M, Lee M, Aglioti SM, Iannetti G. Seeing facial expressions enhances placebo analgesia. Pain. 2014;155: 666–73.
39. Carlino E, Torta D, Piedimonte A, Frisaldi E, Vighetti S, Benedetti F. Role of explicit verbal information in conditioned analgesia. Eur J Pain. 2015;19:546–53.
40. Flaten MA, Bjørkedal E, Lyby PS, Figenschau Y, Aslaksen PM. Failure to find a conditioned placebo analgesic response. Front Psychol. 2018;9:1198.
41. Rhudy JL, Güereca YM, Kuhn BL, Palit S, Flaten MA. The influence of placebo analgesia manipulations on pain report, the nociceptive flexion reflex, and autonomic responses to pain. J Pain. 2018;00:1–18.
42. Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. Pain. 2000;84:65–75.
43. Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F. How the number of learning trials affects placebo and nocebo responses. Pain. 2010;151:430–9.
44. Jensen K, Kaptchuk T, Kirsch I, Raicek J, Lindstrom K, Berna C, et al. Nonconscious activation of placebo and nocebo pain responses. Proc Natl Acad Sci. 2012;109:15959–64.
45. Rhudy JL, Williams AE, McCabe KM, Russell JL, Maynard LJ. Emotional control of nociceptive reactions (ECON): do affective valence and arousal play a role? Pain. 2008;136:250–61.
46. Absi MA, Rokke PD. Can anxiety help us tolerate pain? Pain. 1991;46:43–51.
47. Finn DP, Beckett SRG, Richardson D, Kendall DA, Marsden CA, Chapman V. Evidence for differential modulation of conditioned aversion and fear-conditioned analgesia by CB1 receptors. Eur J Neurosci. 2004;20:848–52.
48. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, et al. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. J Neurosci. 2001;21:9896–903.
49. Rhudy JL, Grimes JS, Meagher MW. Fear-induced hypoalgesia in humans: effects on low intensity thermal stimulation and finger temperature. J Pain. 2004;5:458–68.
50. Colloca L, Benedetti F. Nocebo hyperalgesia: how anxiety is turned into pain. Curr Opin Anaesthesiol. 2007;20:435–9.
51. Benedetti F, Amanzio M, Casadio C, Oliaro A, Maggi G. Blockade of nocebo hyperalgesia by the cholecystokinin antagonist proglumide. Pain. 1997;71:135–40.
52. Benedetti F, Amanzio M, Vighetti S, Asteggiano G. The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. J Neurosci. 2006;26:12014–22.
53. Davis M. The role of the amygdala in fear and anxiety. Annu Rev Neurosci. 1992;15:353–75.
54. Paulus MP, Stein MB. An insular view of anxiety. Biol Psychiatry. 2006;60:383–7.
55. Jensen K, Kaptchuk T, Chen X, Kirsch I, Ingvar M, Gollub R, et al. A neural mechanism for nonconscious activation of conditioned placebo and nocebo responses. Cereb Cortex. 2015;25: 3903–10.
56. Reicherts P, Wiemer J, Gerdes ABM, Schulz SM, Pauli P, Wieser MJ. Anxious anticipation and pain: the influence of instructed vs conditioned threat on pain. Soc Cogn Affect Neurosci. 2017;12: 544–54.
57. Izquierdo I, Furini CRG, Myskiw JC. Fear memory. Physiol Rev. 2016;96:695–750.
58. Maren S. Neurobiology of Pavlovian fear conditioning. Annu Rev Neurosci. 2001;24:897–931.
59. Kong J, Gollub RL, Polich G, Kirsch I, LaViolette P, Vangel M, et al. A functional magnetic resonance imaging study on the neural mechanisms of hyperalgesic nocebo effect. J Neurosci. 2008;28: 13354–62.
60. Atlas LY, Wager TD. How expectations shape pain. Neurosci Lett. 2012;520:140–8.
61. Lau BK, Vaughan CW. Descending modulation of pain: the GABA disinhibition hypothesis of analgesia. Curr Opin Neurobiol. 2014;29:159–64.
62. Rea K, Olango WM, Harhen B, Kerr DM, Galligan R, Fitzgerald S, et al. Evidence for a role of GABAergic and glutamatergic signalling in the basolateral amygdala in endocannabinoid-mediated fear-conditioned analgesia in rats. Pain. 2013;154:576–85.
63. Chance WT, White AC, Krynock GM, Rosecrans JA. Autoanalgesia: behaviorally activated antinociception. Eur J Pharmacol. 1977;44:283–4.
64. Chance WT, White AC, Krynock GM, Rosecrans JA. Conditional fear-induced antinociception and decreased binding of [3H]N-Leu-enkephalin to rat brain. Brain Res. 1978;141:371–4.
65. Davis HD, Hendersen RW. Effects of conditioned fear on responsiveness to pain: long-term retention and reversibility by naloxone. Behav Neurosci. 1985;99:277–89.
66. Lee HJ, Choi J-S, Brown TH, Kim JJ. Amygdalar NMDA receptors are critical for the expression of multiple conditioned fear responses. J Neurosci. 2001;21:4116–24.
67. Helmstetter FJ. Stress-induced hypoalgesia and defensive freezing are attenuated by application of diazepam to the amygdala. Pharmacol Biochem Behav. 1993;44:433–8.
68. Harris JA, Westbrook RF. Effects of benzodiazepine microinjection into the amygdala or periaqueductal gray on the expression of conditioned fear and hypoalgesia in rats. Behav Neurosci. 1995;109:295–304.
69. Harris JA, Westbrook RF. Midazolam impairs the acquisition of conditioned analgesia if rats are tested with an acute but not a chronic noxious stimulus. Brain Res Bull. 1996;39:227–33.
70. De Felice M, Ossipov MH. Cortical and subcortical modulation of pain. Pain Manag. 2016;6:111–20.
71. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. Curr Opin Support Palliat Care. 2014;8:143–51.
72. Bingel U, Lorenz J, Schoell E, Weiller C, Büchel C. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain. 2006;120:8–15.
73. Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J, et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron. 2009;63:533–43.
74. Krummenacher P, Candia V, Folkers G, Schedlowski M, Schönbächler G. Prefrontal cortex modulates placebo analgesia. Pain. 2010;148:368–74.
75. Watson A, El-Deredy W, Iannetti GD, Lloyd D, Tracey I, Vogt BA, et al. Placebo conditioning and placebo analgesia modulate a common brain network during pain anticipation and perception. Pain. 2009;145:24–30.
76. Fox RJ, Sorenson CA. Bilateral lesions of the amygdala attenuate analgesia induced by diverse environmental challenges. Brain Res. 1994;648:215–21.
77. Helmstetter FJ. The amygdala is essential for the expression of conditional hypoalgesia. Behav Neurosci. 1992;106:518–28.
78. Watkins LR, Wiertelak EP, Maier SF. The amygdala is necessary for the expression of conditioned but not unconditioned analgesia. Behav Neurosci. 1993;107:402–5.
79. Merskey H. Bogduk N, Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. 2nd ed. Seattle, WA: IASP Press; 1994.
80. Gentry W, Bernal G. Chronic pain. In: Williams G, Gentry W, editors. Behav approaches medical treatment. Cambridge: Ballinger; 1977. p. 173–82.
81. Klinger R, Matter N, Kothe R, Dahme B, Hofmann UG, Krug F. Unconditioned and conditioned muscular responses in patients with chronic back pain and chronic tension-type headaches and in healthy controls. Pain. 2010;150:66–74.

82. Schneider C, Palomba D, Flor H. Pavlovian conditioning of muscular responses in chronic pain patients: central and peripheral correlates. Pain. 2004;112:239–47.
83. Lethem J, Slade PD, Troup JDG, Bentley G. Outline of a fear-avoidance model of exaggerated pain perception—I. Behav Res Ther. 1983;21:401–8.
84. Vlaeyen JWS, Linton SJ. Fear-avoidance model of chronic musculoskeletal pain: 12 years on. Pain. 2012;153:1144–7.
85. George SZ, Dannecker EA, Robinson ME. Fear of pain, not pain catastrophizing, predicts acute pain intensity, but neither factor predicts tolerance or blood pressure reactivity: an experimental investigation in pain- free individuals. Eur J Pain. 2006;10:457–65.
86. Smeets RJEM, Vlaeyen JWS, Kester ADM, Knottnerus JA. Reduction of pain catastrophizing mediates the outcome of both physical and cognitive-behavioral treatment in chronic low back pain. J Pain. 2006;7:261–71.
87. Turner JA, Jensen MP, Warms CA, Cardenas DD. Catastrophizing is associated with pain intensity, psychological distress, and pain-related disability among individuals with chronic pain after spinal cord injury. Pain. 2002;98:127–34.
88. Turk DC, Wilson HD. Fear of pain as a prognostic factor in chronic pain: conceptual models, assessment, and treatment implications. Curr Pain Headache Rep. 2010;14:88–95.
89. Harvie DS, Moseley GL, Hillier SL, Meulders A. Classical conditioning differences associated with chronic pain: a systematic review. J Pain. 2017;18:889–98.
90. Flor H, Birbaumer N, Roberts LE, Feige B, Lutzenberger W, Hermann C, et al. Slow potentials, event-related potentials, "gamma-band" activity, and motor responses during aversive conditioning in humans. Exp Brain Res. 1996;112:298–312.
91. Icenhour A, Langhorst J, Benson S, Schlamann M, Hampel S, Engler H, et al. Neural circuitry of abdominal pain-related fear learning and reinstatement in irritable bowel syndrome. Neurogastroenterol Motil. 2015;27:114–27.
92. Claassen J, Labrenz F, Ernst TM, Icenhour A, Langhorst J, Forsting M, et al. Altered cerebellar activity in visceral pain-related fear conditioning in irritable bowel syndrome. Cerebellum. 2017;16:508–17.
93. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2163–96.
94. Thomas BL, Cutler M, Novak C. A modified counterconditioning procedure prevents the renewal of conditioned fear in rats. Learn Motiv. 2012;43:24–34.
95. Meulders A, Karsdorp PA, Claes N, Vlaeyen JWS. Comparing counterconditioning and extinction as methods to reduce fear of movement-related pain. J Pain. 2015;16:1353–65.
96. Meulders A, Vansteenwegen D, Vlaeyen JWS. The acquisition of fear of movement-related pain and associative learning: a novel pain-relevant human fear conditioning paradigm. Pain. 2011;152: 2460–9.
97. Vervliet B, Craske MG, Hermans D. Fear extinction and relapse: state of the art. Annu Rev Clin Psychol. 2013;9:215–48.
98. Gramsch C, Kattoor J, Icenhour A, Forsting M, Schedlowski M, Gizewski ER, et al. Learning pain-related fear: neural mechanisms mediating rapid differential conditioning, extinction and reinstatement processes in human visceral pain. Neurobiol Learn Mem. 2014;116:36–45.
99. Icenhour A, Kattoor J, Benson S, Boekstegers A, Schlamann M, Merz CJ, et al. Neural circuitry underlying effects of context on human pain-related fear extinction in a renewal paradigm. Hum Brain Mapp. 2015;36:3179–93.
100. Kattoor J, Gizewski ER, Kotsis V, Benson S, Gramsch C, Theysohn N, et al. Fear conditioning in an abdominal pain model: neural responses during associative learning and extinction in healthy subjects. PLoS One. 2013;8:e51149.
101. Maeda Y, Kan S, Fujino Y, Shibata M. Verbal instruction can induce extinction of fear of movement-related pain. J Pain. 2018;19:1063–73.
102. Hermans D, Craske MG, Mineka S, Lovibond PF. Extinction in human fear conditioning. Biol Psychiatry. 2006;60:361–8.
103. Monfils M-H, Cowansage KK, Klann E, LeDoux JE. Extinction-reconsolidation boundaries: key to persistent attenuation of fear memories. Science. 2009;324:951–5.
104. Lee JLC, Nader K, Schiller D. An update on memory reconsolidation updating. Trends Cogn Sci. 2017;21:531–45.
105. Nader K. Reconsolidation and the dynamic nature of memory. Cold Spring Harb Perspect Biol. 2015;7:a021782.
106. Kindt M, Soeter M, Vervliet B. Beyond extinction: erasing human fear responses and preventing the return of fear. Nat Neurosci. 2009;12:256–8.
107. Chan JCK, LaPaglia JA. Impairing existing declarative memory in humans by disrupting reconsolidation. Proc Natl Acad Sci. 2013;110:9309–13.
108. Escosteguy-Neto JC, Varela P, Correa-Neto NF, Coelho LS, Onaivi ES, Santos-Junior JG. Reconsolidation and update of morphine-associated contextual memory in mice. Neurobiol Learn Mem. 2016;130:194–201.
109. Nader K, Schafe GE, Le Doux JE. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature. 2000;406:722–6.
110. Schiller D, Monfils M-H, Raio CM, Johnson DC, LeDoux JE, Phelps EA. Preventing the return of fear in humans using reconsolidation update mechanisms. Nature. 2010;463:49–53.
111. Steinfurth ECK, Kanen JW, Raio CM, Clem RL, Huganir RL, Phelps EA. Young and old Pavlovian fear memories can be modified with extinction training during reconsolidation in humans. Learn Mem. 2014;21:338–41.
112. Xue Y, Luo Y, Wu P, Shi H, Xue L, Chen C, et al. A memory retrieval-extinction procedure to prevent drug craving and relapse. Science. 2012;336:241–5.
113. Agren T. Human reconsolidation: a reactivation and update. Brain Res Bull. 2014;105:70–82.
114. Colagiuri B, Quinn VF. Autonomic arousal as a mechanism of the persistence of nocebo hyperalgesia. J Pain. 2018;19:476–86.
115. Colagiuri B, Quinn VF, Colloca L. Nocebo hyperalgesia, partial reinforcement, and extinction. J Pain. 2015;16:995–1004.
116.• Quinn VF, Colagiuri B. Using learning strategies to inhibit the nocebo effect. Colloca L, editor. Int Rev Neurobiol. Cambridge, MA: Academic Press; 2018. p. 307–27. https://doi.org/10.1016/bs.irn.2018.01.011. **A very good review discussing how to exploit learning strategies to inhibit the nocebo effect.**
117. Lubow RE. Latent inhibition. Psychol Bull. 1973;79:398–407.
118. Klosterhalfen S, Kellermann S, Stockhorst U, Wolf J, Kirschbaum C, Hall G, et al. Latent inhibition of rotation chair-induced nausea in healthy male and female volunteers. Psychosom Med. 2005;67: 335–40.
119. Quinn VF, Livesey EJ, Colagiuri B. Latent inhibition reduces nocebo nausea, even without deception. Ann Behav Med. 2017;51:432–41.
120. Hall G, Stockhorst U, Enck P, Klosterhalfen S. Overshadowing and latent inhibition in nausea-based context conditioning in humans: theoretical and practical implications. Q J Exp Psychol. 2016;69:1227–38.
121. Stockhorst U, Hall G, Enck P, Klosterhalfen S. Effects of overshadowing on conditioned and unconditioned nausea in a rotation paradigm with humans. Exp Brain Res. 2014;232: 2651–64.

122. Stockhorst U, Wiener JA, Klosterhalfen S, Klosterhalfen W, Aul C, Steingrüber H-J. Effects of overshadowing on conditioned nausea in cancer patients: an experimental study. Physiol Behav. 1998;64:743–53.
123. Jenkins WO, Stanley JC. Partial reinforcement: a review and critique. Psychol Bull. 1950;47:193–234.
124. Coccoz V, Maldonado H, Delorenzi A. The enhancement of reconsolidation with a naturalistic mild stressor improves the expression of a declarative memory in humans. Neuroscience. 2011;185:61–72.
125. Coccoz V, Sandoval AV, Stehberg J, Delorenzi A. The temporal dynamics of enhancing a human declarative memory during reconsolidation. Neuroscience. 2013;246:397–408.
126. Vlaeyen JWS, de Jong J, Sieben J, Crombez G. Graded exposure in vivo for pain-related fear. Psychol Approaches Pain Manag Pract Handb. 2nd ed. New York: The Guilford Press; 2002. p. 210–33.
127. Boersma K, Linton S, Overmeer T, Jansson M, Vlaeyen JWS, de Jong J. Lowering fear-avoidance and enhancing function through exposure in vivo: a multiple baseline study across six patients with back pain. Pain. 2004;108:8–16.
128. Flink IK, Nicholas MK, Boersma K, Linton SJ. Reducing the threat value of chronic pain: a preliminary replicated single-case study of interoceptive exposure versus distraction in six individuals with chronic back pain. Behav Res Ther. 2009;47:721–8.
129. de Jong JR, Vlaeyen JWS, Onghena P, Goossens MEJB, Geilen M, Mulder H. Fear of movement/(re)injury in chronic low back pain: education or exposure in vivo as mediator to fear reduction? Clin J Pain. 2005;21:9–17.
130. Leeuw M, Goossens MEJB, van Breukelen GJP, de Jong JR, Heuts PHTG, Smeets RJEM, et al. Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. Pain. 2008;138:192–207.
131. Vlaeyen JWS, de Jong J, Geilen M, Heuts PHTG, van Breukelen G. Graded exposure in vivo in the treatment of pain-related fear: a replicated single-case experimental design in four patients with chronic low back pain. Behav Res Ther. 2001;39:151–66.
132. Woods MP, Asmundson GJG. Evaluating the efficacy of graded in vivo exposure for the treatment of fear in patients with chronic back pain: a randomized controlled clinical trial. Pain. 2008;136: 271–80.
133. de Jong JR, Vlaeyen JWS, Onghena P, Cuypers C, den Hollander M, Ruijgrok J. Reduction of pain-related fear in complex regional pain syndrome type I: the application of graded exposure in vivo. Pain. 2005;116:264–75.
134. de Jong JR, Vlaeyen JWS, van Eijsden M, Loo C, Onghena P. Reduction of pain-related fear and increased function and participation in work-related upper extremity pain (WRUEP): effects of exposure in vivo. Pain. 2012;153:2109–18.
135. Linton SJ, Boersma K, Jansson M, Overmeer T, Lindblom K, Vlaeyen JWS. A randomized controlled trial of exposure in vivo for patients with spinal pain reporting fear of work-related activities. Eur J Pain. 2012;12:722–30.
136. Flor H. The functional organization of the brain in chronic pain. Prog Brain Res. 2000;129:313–22.
137. Kuner R, Flor H. Structural plasticity and reorganisation in chronic pain. Nat Rev Neurosci. 2017;18:20–30.
138. Moseley GL, Flor H. Targeting cortical representations in the treatment of chronic pain: a review. Neurorehabil Neural Repair. 2012;26:646–52.
139. Flor H, Denke C, Schaefer M, Grüsser S. Effect of sensory discrimination training on cortical reorganisation and phantom limb pain. Lancet. 2001;357:1763–4.
140. Wakolbinger R, Diers M, Hruby LA, Sturma A, Aszmann OC. Home-based tactile discrimination training reduces phantom limb pain. Pain Pract. 2018;18:709–15.
141. Barker KL, Elliott CJ, Sackley CM, Fairbank JC. Treatment of chronic back pain by sensory discrimination training. A phase I RCT of a novel device (FairMed) vs. TENS. BMC Musculoskelet Disord. 2008;9:97.
142. Trapp W, Weinberger M, Erk S, Fuchs B, Mueller M, Gallhofer B, et al. A brief intervention utilising visual feedback reduces pain and enhances tactile acuity in CLBP patients. J Back Musculoskelet Rehabil. 2015;28:651–60.
143. Wand BM, Abbaszadeh S, Smith AJ, Catley MJ, Moseley GL. Acupuncture applied as a sensory discrimination training tool decreases movement-related pain in patients with chronic low back pain more than acupuncture alone: a randomised cross-over experiment. Br J Sports Med. 2013;47:1085–9.
144. Moseley GL, Wiech K. The effect of tactile discrimination training is enhanced when patients watch the reflected image of their unaffected limb during training. Pain. 2009;144:314–9.
145. Moseley GL, Zalucki NM, Wiech K. Tactile discrimination, but not tactile stimulation alone, reduces chronic limb pain. Pain. 2008;137:600–8.
146. Pleger B, Tegenthoff M, Ragert P, Förster A-F, Dinse HR, Schwenkreis P, et al. Sensorimotor returning in complex regional pain syndrome parallels pain reduction. Ann Neurol. 2005;57: 425–9.
147. Schmid AC, Schwarz A, Gustin SM, Greenspan JD, Hummel FC, Birbaumer N. Pain reduction due to novel sensory-motor training in complex regional pain syndrome I – a pilot study. Scand J Pain. 2017;15:30–7.
148. Nir RR, Yarnitsky D, Honigman L, Granot M. Cognitive manipulation targeted at decreasing the conditioning pain perception reduces the efficacy of conditioned pain modulation. Pain. 2012;153:170–6.
149. Fazio RH, Olson MA. Implicit measures in social cognition research: their meaning and use. Annu Rev Psychol. 2003;54:297–327.
150. Gawronski B, Hofmann W, Wilbur CJ. Are "implicit" attitudes unconscious? Conscious Cogn. 2006;15:485–99.
151. Melnikoff DE, Bargh JA. The mythical number two. Trends Cogn Sci. 2018;22:280–93.
152. Carew TJ, Hawkins RD, Kandel ER. Differential classical conditioning of a defensive withdrawal reflex in Aplysia californica. Science. 1983;219:397–400.
153. Berntson GG, Tuber DS, Ronca AE, Bachman DS. The decerebrate human: associative learning. Exp Neurol. 1983;81:77–88.
154. Grau JW, Salinas JA, Illich PA, Meagher MW. Associative learning and memory for an antinociceptive response in the spinalized rat. Behav Neurosci. 1990;104:489–94.
155. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD- 11. Pain. 2015;156: 1003–7.