Abstract: The role of pain-related fear learning and memory processes, conceptually embedded within the fear-avoidance model of chronic pain, is increasingly recognized. The unique biological salience of interoceptive, visceral pain with its cognitive, emotional, and motivational facets fosters associative learning. Conditioned fear is in principle adaptive but may turn maladaptive and contribute to hypervigilance and hyperalgesia in chronic pain. This review summarizes current knowledge on the formation, extinction, and return of pain-related memories with a focus on visceral pain. It provides a conceptual background, describes experimental approaches, and summarizes findings on behavioral and neural mechanisms in healthy humans and patients with chronic pain. Future directions underscore the potential of refining knowledge on the role of associative learning in the pathophysiology and treatment of chronic visceral pain in disorders of gut–brain interactions such as irritable bowel syndrome.

Keywords: fear-avoidance model; fear conditioning and extinction; irritable bowel syndrome; pain-related fear; visceral pain.


Schlüsselwörter: Furchtvermeidungsmodell; Furchtkonditionierung und Extinktion; Reizdarmsyndrom; schmerzassozierte Furcht; viszeraler Schmerz.

Visceral pain and gut feelings

Pain is a ubiquitous and uniquely aversive experience that is much more than merely an unpleasant sensation. It rather encompasses complex sensory, cognitive, emotional, and motivational components that are ultimately part of an evolutionarily driven adaptive response aimed at self-protection and survival (Lumley et al., 2011). Given its biological significance as a signal indicating bodily harm, it is not surprising that pain is universally feared and may literally be “hard to forget”. Indeed, virtually every one of us can readily recall previous painful episodes, even if they occurred years or decades ago. We are hence “hardwired” to fear and strive to avoid pain, with pain-related fear as the key emotional response essential to triggering adaptive behavior in the face of pain. However, fear can also turn maladaptive and contribute to the pathophysiology of chronic pain. Chronic pain is a major and unresolved healthcare problem with significant individual as well as societal implications.
From fear to avoidance

Dynamic learning and memory processes shape the emergence and persistence of pain-related fear in anticipation of imminent pain. Embedded within the influential fear-avoidance model (Figure 1), classically conditioned pain-related fear is considered to contribute to pain chronification (Vlaeyen, 2015), including chronic visceral pain (Elsenbruch and Labrenz, 2018). Within this framework, several mechanisms, including conditioned changes in perceptual and attentional processes, have been proposed (Vlaeyen, 2015; Zaman et al., 2015) in keeping with the crucial role of hyperalgesia and hypervigilance in the pathophysiology and treatment of chronic pain. Support comes from experimental findings demonstrating altered fear acquisition across different chronic pain conditions (Vlaeyen, 2015), including IBS (Claassen et al., 2017; Icenhour et al., 2015b; Labus et al., 2013). Evidence suggesting deficient safety learning in patients has also emerged (Icenhour et al., 2015b; Meuldens et al., 2014), which is interesting as it could reinforce maladaptive safety-seeking as a key component of avoidance behavior (Crombez et al., 2012). Finally, clinical trials testing exposure-based interventions for chronic pain show promising results (e.g., Craske et al., 2011; Linton et al., 2008; Ljótsson et al., 2014), although long-term symptom relief remains difficult to achieve. As in anxiety- and stress-related disorders, overcoming the risk of relapse and treatment failure remains a challenge. Improving knowledge about mediators and moderators of pain-related extinction learning is therefore essential, not only in the context of treatment for chronic pain but also as a fundamental aspect of adaptive human behavior.

Extinction and beyond

Extinction of conditioned fear responses to a former threat-predictive cue is an adaptive process when this threat is no longer present, allowing behavioral flexibility in rapidly changing, complex environments. However, the initially acquired memory trace is not erased during extinction learning but can be reactivated, as evidenced by
spontaneous recovery, savings, renewal, and reinstatement phenomena (Bouton, 2004). Resurging fear poses a major challenge in cognitive-behavioral treatment approaches, especially exposure therapy, which is essentially built on robust extinction of fear. Impaired extinction efficacy hence implies a latent vulnerability for fear memory reactivation and relapse. Indeed, impaired extinction efficacy of maladaptive pain-related fear and safety responses, including reinstatement of pain-related fear, has already been observed in patients with chronic pain (Icenhour et al., 2015b; Labus et al., 2013; Meulders et al., 2017; Schneider et al., 2004), which would fit within but also considerably extend the fear-avoidance model of pain. This is not only conceptually intriguing, yet calls for experimental studies to further elucidate the formation and especially the extinction of pain-related fear and safety learning in a clinically relevant context.

Unraveling the acquisition and extinction of pain-related fear in experimental settings

Pavlovian fear conditioning as a translational model in the neurosciences has proven highly fruitful for investigating associative learning and extinction processes involving aversive stimuli (Milad and Quirk, 2012), including pain (Vlaeyen, 2015). At the interface of the cognitive neurosciences and the visceral pain field, innovative experimental paradigms with visceral stimuli as unconditioned stimuli (US) and/or conditioned stimuli (CS) have been introduced (Ceunen et al., 2016; Gramsch et al., 2014; Icenhour et al., 2015a, 2017; Schneider et al., 2018). Across the board, a robust extinction of fear was observed in patients with chronic pain (Icenhour et al., 2015b; Labrenz et al., 2016). Within the brain, CS–US pairings consistently evoked an increase in negative emotional valence of pain-predictive conditioned stimuli (CS’) when compared with unpaired cues (CS) (Gramsch et al., 2014; Icenhour et al., 2015a; Kattoor et al., 2013; Koenen et al., 2018; Labrenz et al., 2016). Within the brain, CS’ relative to CS’ recruited key regions of the central fear network, including amygdala, as well as the anterior cingulate cortex and insula as core nodes of the salience network with well-established roles in the integration of interoceptive signals with emotional and cognitive input (Menon and Uddin, 2010). At the same time, cues signaling the absence of impending pain (i.e., CS’) acquired separate emotional value and neural signature, in line with their role as safety signals. While distinct neural processing of CS does not appear to be specific to pain-related conditioning (Fullana et al., 2016), it may bear special relevance in chronic pain as a mechanism underlying maladaptive avoidance behavior, particularly regarding interoceptive, visceral pain (Koenen et al., 2018).

During extinction, unpaired CS presentations reproducibly resulted in a return of cue valence to baseline levels, accompanied by accurate contingency ratings, and differential neural responses particularly involving prefrontal regions (Icenhour et al., 2015a; Kattoor et al., 2013). In keeping with the notion that the excitatory memory trace is preserved rather than erased (Bouton, 2004), we were further able to induce a reinstatement effect by unexpected and unsignaled confrontation with visceral pain stimuli (Gramsch et al., 2014; Kattoor et al., 2013, 2014). Interestingly, the involvement of the hippocampus as a central mediator of this effect was more pronounced in patients with IBS (Icenhour et al., 2015b). We finally observed that extinction in the visceral conditioning model is context-dependent (Icenhour et al., 2015a), in line with evidence from the broader field of inhibitory learning (Bouton, 2004). Interestingly, a context change affected particularly differential neural responses to conditioned safety cues, further supporting the distinct relevance of safety learning and memory processes related to visceral pain.

Predictability and contingency awareness

Several cognitive and emotional factors likely shape the successful formation of conditioned pain-related fear and safety not only in healthy individuals but also in patients with chronic pain. These include predictability as well as the conscious awareness of CS–US contingencies – aspects that remain incompletely understood in the context of pain. In light of first data supporting altered contingency learning and extinction in patients with chronic pain (Icenhour et al., 2015b; Meulders et al., 2014), we elucidated the putative role of contingency awareness in shaping the acquisition and extinction of conditioned emotional responses in a large sample of healthy volunteers (Labrenz et al., 2015). Herein, participants with highly accurate contingency awareness revealed greater emotional learning toward both danger as well as safety cues. They further demonstrated full extinction of pain-predictive cue unpleasantness, while exhibiting persistent positive emotional responses to safety signals. Moreover,
contingency accuracy predicted conditioned positive emotional responses to safety cues, while no predictive value was found for danger cues after acquisition. These findings suggest contingency accuracy to distinctly impact learned emotional responses to safety and danger cues.

To address the role of predictability in visceral pain-related fear acquisition and to elucidate its underlying neural mechanisms (Labrenz et al., 2016), we compared healthy individuals undergoing differential fear conditioning involving contingent CS–US pairings (predictable group) with a group experiencing noncontingent presentations of CS and US (unpredictable group). Successful differential learning of pain-related fear and safety was exclusively observed in the classically conditioned predictable group, whereas the unpredictable group perceived both cues experienced during acquisition as danger signals. Intriguingly, predictability as an inherent feature of contingent pairings appears to shape neural responses to the US, which is an entirely novel aspect. Specifically, the unpredictable group revealed enhanced US-related activation in brain regions related to the encoding and modulation of pain, including the prefrontal and somatosensory regions, the insular cortex, and the periaqueductal gray. These observations suggest the experience of unpredictable visceral pain to contribute to a generalized acquisition of putative danger cues.

Together, these findings underscore classically conditioned predictability and awareness of contingencies regarding cues predicting imminent threat but also safety to constitute key moderators of visceral pain-related fear learning and memory processes. Conditioning with interoceptive visceral stimuli appears to not only yield differential anticipatory activation but demonstrably also affects subsequent visceroceptive processing (Icenhour et al., 2017; Labrenz et al., 2016). As a consequence of differential conditioning, neural activation in response to equally intense, nonpainful rectal distensions was observed to evoke greater activation in prefrontal and cingulate regions associated with processes of attention and appraisal when cued by previously conditioned threat–predictive CS compared with conditioned safety predictors (Icenhour et al., 2017). Together with comparable US intensity ratings, these findings lend first support for the notion that visceral pain-related fear induced by prior learning may particularly contribute to visceral hypervigilance (Figure 1). Ultimately, in patients suffering from chronic visceral pain, environmental signals, but also internal and external contexts, including stress, may be readily associated with frequently experienced symptoms in the absence of full awareness, yielding visceral sensations an unpredictable threat and possibly contributing to an overestimation of true contingencies.

From stress to elucidating interindividual differences: the road to personalized interventions?

Stress plays a major role in the etiology and pathophysiology of chronic visceral pain (Labanski et al., 2020) and has well-documented effects on emotional learning and memory processes (Elsenbruch and Wolf, 2015). However, the role of acute or chronic stress and stress mediators in shaping pain-related fear remains unknown. To elucidate the potential impact of the acute stress mediator cortisol on pain-related fear, we recently conducted a randomized, double-blind, placebo-controlled study in healthy volunteers (Benson et al., 2019). We tested the effects of pharmacologically increased cortisol levels on the acquisition and extinction of pain-related fear comparing conditioned responses to cues predicting visceral and somatic pain stimuli applied as US. We could demonstrate that conditioned pain-related fear was significantly reduced after hydrocortisone application for the visceral, but not somatic modality, suggesting that elevated cortisol levels may distinctly interfere with pain-related emotional learning in the context of visceral pain.

In addition to altered stress responsivity to acute challenges in patients with chronic visceral pain involving the release and direct effects of cortisol (Labanski et al., 2020), chronic stress constitutes a major burden in patients and an important risk factor for disease onset and symptom exacerbation. Whether chronic stress impacts pain-related emotional learning and memory remains to be elucidated. First evidence of chronic stress as a possible moderator of memory processes in the context of visceroception, however, was recently established in a study elucidating the putative link between perceived chronic stress burden and various facets of visceroception in a large sample of healthy men and women (Icenhour et al., 2020). Results supported that chronic stress not only increased the feeling of defecatory urgency induced by rectal distensions as a particularly troublesome visceral symptom with a profound emotional dimension but was also associated with a memory bias for visceral sensations. Specifically, highly stressed individuals recalled more intense feelings of urgency than participants reporting low levels of stress, as well as relative to their initial
perception (Icenhour et al., 2020). Together, these findings lend further support to the notion that persisting interoceptive hypervigilance may be distinctly shaped not only by the salience of visceral pain (Koenen et al., 2018) but also by acute and chronic stress.

Stress is an important yet not the only putative source of interindividual variability in the acquisition, extinction, and return of learned emotional responses (Lonsdorf and Merz, 2017), including pain-related fear. As a crucial psychological modulator, anxiety likely also plays a pivotal role. Anxiety not only demonstrably affects pain-related memory formation and reinstatement in patients with IBS (Icenhour et al., 2015b) but was also recently linked to aberrant neurotransmitter levels and altered functional connectivity in patients with chronic visceral pain, particularly involving the medial prefrontal cortex as a key hub of the extinction network (Icenhour et al., 2019). Together, a complex interplay between psychological traits, including anxiety, cognitive biases, stress, and stress reactivity, and biological factors such as age, sex, stress hormones, and brain morphology may increase the vulnerability for altered pain-related learning and memory processes, which likely contribute to the transition from acute to chronic pain. Ultimately, identifying moderators and mediators of pain-related fear learning and extinction and elucidating mechanisms underlying extinction efficacy using reinstatement or renewal paradigms may help to unravel variability in extinction learning and long-term efficacy relevant to the pathophysiology and treatment of numerous conditions associated with recurring visceral symptoms, particularly disturbances of gut–brain interaction.

Author contribution: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: This study was supported by the Deutsche Forschungsgemeinschaft (DFG) through the research unit FOR 1581 (P7) and the collaborative research center SFB 1280 (project number 316803389; A10, A12).

Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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