From fear of movement-related pain and avoidance to chronic pain disability: A state of the art review

Ann Meulders[1,2]

[1] Research Group Health Psychology, KU Leuven, Leuven, Belgium

[2] Experimental Health Psychology, Department of Clinical Psychological Science, Maastricht University, The Netherlands

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Author note

Correspondence concerning this article should be addressed to Ann Meulders, PhD, Faculty of Psychology and Educational Sciences, Research Group Health Psychology, KU Leuven, Tiensestraat 102, box 3726, 3000 Leuven, Belgium. E-mail: ann.meulders@kuleuven.be, T: +32 (0)16 32 60 38, F: +32 (0)16 32 61 44.

Abstract

This review addresses recent developments in fear of movement-related pain and avoidance research, adopting a contemporary learning approach focusing on cognitive, emotional, and behavioral factors, and emphasizing the role of the motivational context including pain-avoidance goals but also other valued life goals. We particularly demonstrated the role of classical conditioning in the acquisition, generalization and extinction of fear of movement-related pain, and how safety-seeking behavior during exposure-based treatment may hamper genuine extinction causing relapse. We further highlighted the importance of newly developed methods to study operant conditioning of behavioral avoidance itself, and its relationship with individual vulnerability factors (e.g. catastrophizing) and resiliencies (e.g. positive affect) to further our understanding of mechanisms underlying the development and persistence of chronic pain disability.

1. Introduction

Pain is a biologically salient signal and adaptive response to bodily threat that prompts protective action. The protective response repertoire initially includes increased arousal, selective attention, escape, and painful facial expressions, as well as long-term recuperative avoidance and safety-seeking behaviors. Pain is thus a *motivational state* initiating early defensive responses followed by recuperative behaviors aimed to promote recovery. Given its intrinsically alarming function, pain is a potent motivator for learning –it stimulates the detection of stimuli predicting the occurrence of pain and bodily threat in order to avoid or minimize their impact. Pavlovian or classical conditioning is the prime mechanism underlying the prediction of potentially harmful stimuli in the environment[38; 43]. When pairing an initially neutral stimulus (conditioned stimulus; CS) with an aversive outcome (unconditioned stimulus; US), this stimulus in itself may start to elicit defensive responses (conditioned response; CR).

Contemporary fear-avoidance models of chronic musculoskeletal pain advance pain-related fear and avoidance as key contributors to the transition from acute to chronic pain[44; 45]. Catastrophic misinterpretations of pain as being harmful may give rise to pain-related fear, which in turn can initiate avoidance behavior intended to avert bodily threat. When protective action serves to reduce genuine bodily threat, it is highly adaptive, but when pain persists beyond healing time and turns chronic, it may paradoxically increase suffering and disability (Figure 1). In this paper, we will review the role of learning mechanisms in the development, spreading, and persistence of fear of movement-related pain and avoidance, and how they contribute to pain-related disability.

Figure 1. Fear-avoidance model of pain.
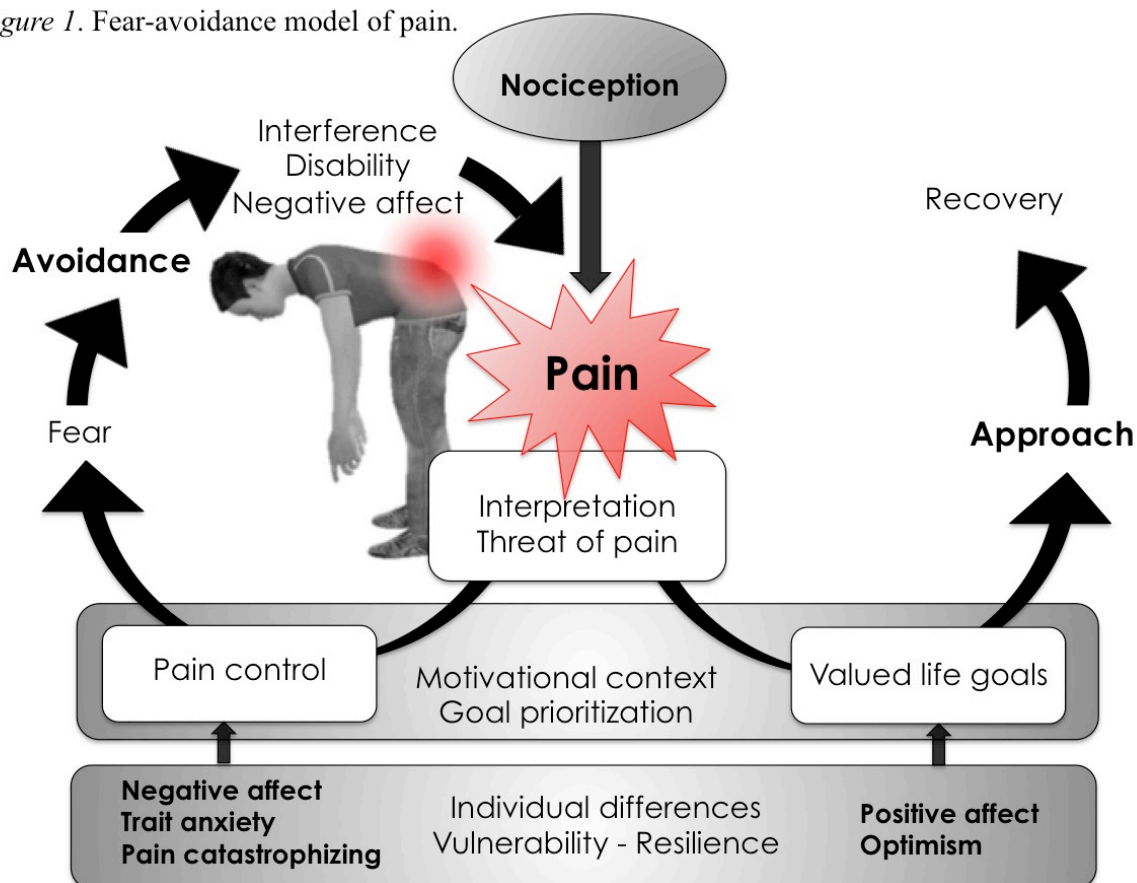
2. The role of learning in pain-related fear and avoidance

2.1. The acquisition of pain-related fear

Due to its biological significance, pain can be considered a US, which by itself triggers protective responses such as psychophysiological arousal (e.g., elevated startle responses, skin conductance, and muscle tone) and escape behavior. Diverse stimuli can precede pain and thus serve as CSs including exteroceptive (tactile, visual, auditory), interoceptive (visceral, olfactory), and proprioceptive stimuli (movement, posture). For patients with musculoskeletal pain, proprioceptive information is particularly relevant to predict pain episodes. For example, a neutral movement (e.g., bending to pick something up) preceding a pain episode (e.g., shooting back pain) may come to signal bodily harm and elicit *fear of movement-related pain* and spur avoidance behavior (Figure 2). So far, we have described situations in which discrete cues predict pain-onset, typically inducing *cued pain-related fear*. Some patients however report spontaneous pain flare-ups without cues predicting the (increases

in) pain[18]. In situations of apparent unpredictable pain, long-lasting contextual cues may be considered predictors of pain, leading to *contextual pain-related fear*. Meulders et al.[33] argued that translated to chronic pain conditions, cued pain-related fear (i.e. predictable pain) and chronic contextual pain-related fear (i.e. unpredictable pain) respectively model regional pain syndromes (e.g., low back pain) and widespread pain such as fibromyalgia.

Figure 2. Fear of movement-related pain acquisition and generalization.
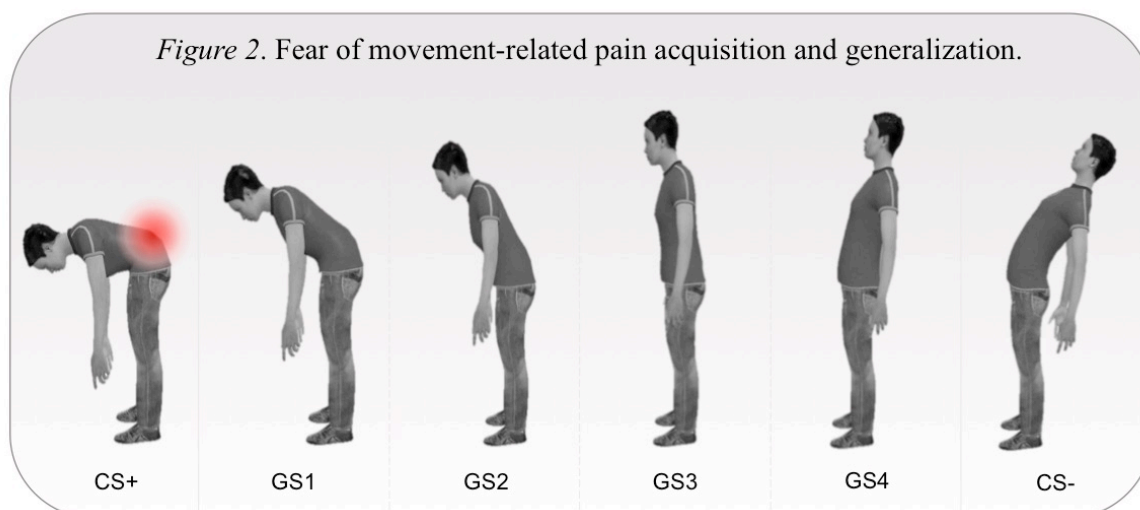
Note – The red radiating dot represents a shooting back pain (i.e. pain-US). During acquisition bending forward (CS+) is the movement that is followed by the pain-US, whereas leaning backward (CS-) is the movement that is not followed by the pain-US. The generalization stimuli (GSs) are novel intermediate movements between the CS+ and the CS-.

Cumulating experimental evidence supports the role of associative learning processes in the acquisition of both cued and contextual pain-related fear. Meulders et al.[34] developed a voluntary joystick movement paradigm to model pain-related fear in musculoskeletal pain disorders: in the predictable condition, neutral joystick movements (moving to left/right) served as CSs of which one direction predicted the painful electrocutaneous stimulus (pain-US); in the unpredictable condition, two other joystick movements (moving upwards/downwards) were never followed by pain. Results showed that the CS+ movement elicited elevated startle amplitudes, increased self-reported fear, and larger response latencies (as a proxy of behavioral avoidance) than the CS- movements. No such differences occurred for both unpredictable CSs, but fear accrued to the context (i.e. increased startle responses during the intertrial interval). Furthermore, we demonstrated similar conditioned responses to the mere intention to perform pain-associated movements, before actually performing these

movements[36], suggesting that *imagining a painful movement* can activate the memory representation of the movement-pain association and in turn evoke conditioned fear[26]. Other evidence supports the idea that pain-related fear can be acquired without direct experience, for example through observation and instruction[13; 16; 19], by symbolically representing pain[17] or by virtue of derived relationships with pain such as conceptual equivalence between stimuli[2; 22].

2.2. The generalization of pain-related fear

Learning which stimuli predict bodily threat is highly adaptive. Nevertheless, adaptive learners face the challenge of how to deal with variations in the appearances of signaling stimuli. Rapid adaptation to a dynamic environment requires balancing discrimination and generalization towards novel situations. *Stimulus generalization*[7] allows extrapolation of the predictive value of one stimulus to novel stimuli (generalization stimuli, GSs) based on (non-)perceptual similarities minimizing the necessity to learn everything anew. Unbridled fear generalization to safe situations may lead to sustained anxiety and excessive avoidance behavior initiating a pathway towards disability[27].

Using the voluntary joystick movement paradigm, we demonstrated that healthy participants were more afraid of and showed elevated startle responses to movements that resembled the original CS+ compared to those resembling the CS-[33; 35]; in the unpredictable condition, however fear generalized in a nondifferential way to all novel movements. In contrast with healthy controls, fibromyalgia patients showed nondifferential generalization in both conditions, suggesting that all GSs triggered strong conditioned responses, irrespective of the previous learning history[15; 27]. Patients showed excessive fear to safe stimuli (GSs resembling the CS-) rather than to those resembling the threatening CS+, suggesting that *impaired safety learning* drives this "overgeneralization" effect. In addition, after receiving disconfirming information during an extinction of generalization phase (i.e. GSs without US), healthy participants quickly update their beliefs leading to extinction of generalized fear whereas fibromyalgia patients continued to display elevated pain-related fear and expectancy to the unreinforced GSs[28].

Similar "overgeneralization" effects exist in expectancy judgments of chronic unilateral hand pain patients in a contingency learning task[25]. Other evidence supporting the lack of selective learning in fibromyalgia patients stems from a clinical diary scenario study using a *blocking* design in which diary entries of a fictitious patient served as CSs and verbal outcomes "pain"/"no pain" as US[23]. First, one cue (Kim was stressed; A+) is paired with "pain". Next, another cue (Kim slept badly; X), referred to as the *blocked stimulus*, presented in compound with the original pain-associated cue is also paired with "pain" (AX+). During the crucial test of X alone, conditioned responding is typically weak or *blocked*, despite previous pairings with the US, because A suffices to predict the occurrence of the US. Compared to healthy controls, fibromyalgia patients did not show blocking to X.

Humans also can abstract conceptual details during a learning episode, which allows them to generalize fear to physically dissimilar stimuli that are semantically related, a process known as *category-based fear conditioning*[6]. Using an adapted version of the voluntary joystick movement paradigm, we paired exemplars from one action category with pain (e.g. "opening" a small, rectangular, blue box with a left joystick movement) and observed fear generalization to conceptually similar exemplars (e.g. "opening" a large, round, yellow box with a right joystick movement), but not to novel exemplars of another action category (e.g. "closing" a small, round, green box with a left joystick movement)[32]. Bennett et al.[2] provided further support for non-perceptual generalization by showing that pain-related fear transferred from nonsense word CSs to joystick movements that were never paired with pain themselves but were trained to belong to the same stimulus equivalence category as the CSs.

2.3. *Extinction and return of pain-related fear*

When the CS is no longer followed by the US (or its mental representation), the CS loses its predictive value and will no longer evoke conditioned responses. *Extinction* is a fragile and context-dependent process[42]. It is commonly accepted that extinction does not erase the original CS-US association, but that a new extinction memory is formed that inhibits the behavioral expression of the

first-learned association. Intact acquisition memory is evidenced by the return of fear when the CS is encountered in a different context than the extinction context (i.e. renewal). Also unexpected encounters with the original pain-US (reinstatement)[5] such as pain flare-ups or other unanticipated non-pain stressors (cross-US reinstatement)[30] can restore pain-related fear. In addition, another challenge is the generalization of the extinction to novel but similar movements and other contexts. Research in back pain patients showed that exposure to physical movement did not generalize to novel dissimilar movements, suggesting that under-generalization of extinction may contribute as well to the maintenance of chronic pain disability [12].

Exposure in vivo is the clinical analogue of Pavlovian extinction and has been effectively used in patients with chronic musculoskeletal pain[46] such as low back pain[10; 11] and CRPS[4]. In essence, this treatment entails confrontation with feared movement/activity, following an idiosyncratic fear hierarchy, until fear is reduced and daily functioning can be resumed. Notwithstanding the success of exposure to reduce pain-related fear and disability, relapse often occurs. The use of *safety-seeking behavior* during exposure (e.g. bending to pick something up with a straight back) has been theorized to impede fear extinction[21]. The idea is that when safety-seeking behavior is performed during extinction, the non-occurrence of the US can be attributed to this safety-seeking behavior hampering genuine extinction learning. However, there is a current debate as to whether allowing judicious safety behavior facilitates or jeopardizes treatment. According to a recent meta-analysis this question remains unsettled[31] highlighting the need for systematic replications with sufficient statistical power and large sample sizes, using idiosyncratic safety-seeking behavior (not predetermined by the experimenter) and taking the motivational context into account. Current recommendations regarding the use of safety-seeking behavior in clinical practice should therefore be interpreted with caution.

We investigated whether performing an avoidance response would hamper extinction of fear of movement-related pain using a voluntary joystick movement paradigm[48]. During extinction, the safety group was instructed that they could avoid the US by pressing a "safety button" on the joystick during the pain-associated movement, whereas a control group did not have this option. When the

avoidance option was eliminated during the subsequent test, return of fear of movement-related pain was observed in the safety group, but not in the control group, demonstrating *protection from extinction.* A follow-up study showed that the same behavior only reliably led to return of fear when the response was serving a pain-avoidance goal (avoiding the US), not when it was serving an achievement goal (attaining a reward)[49], underscoring the importance of the motivational context in understanding the role of safety-seeking behavior in exposure-based interventions.

2.4. The relationship between fear and avoidance in a motivational context

Avoidance is defined as overt behavior aimed to prevent the occurrence of a threatening event (e.g. pain), and the relief experienced when the anticipated catastrophe does not occur has been advanced as a reinforcer of this behavior[47]. Experimental research mainly focused on self-report and psychophysiological correlates of pain-related fear, leaving its behavioral component poorly understood. The lack of scientific attention for avoidance behavior itself is based on the tacit assumption that fear is the sole motivator of avoidance[20] implying that extinguishing fear (i.e. exposure to the feared stimulus without avoidance option) would suffice to abolish avoidance behavior, a procedure referred to as *response prevention with extinction* or *flooding*[37]. However, increasing evidence suggests that there is no one-to-one relationship between fear and avoidance, insinuating that more complex decision-making may be at play, involving weighing the value of pain avoidance against other life goals (e.g. going to work)[50]. Indeed pain-related fear typically occurs in a context of multiple, competing goals. Recent experimental research demonstrated that avoidance behavior, but not fear can be attenuated when another valued, competing goal (i.e. attaining a monetary reward) is introduced[3]. Pain-related fear induces discomfort but does not necessarily lead to disability, therefore the role of behavioral avoidance is essential in explaining the pathway to disability, highlighting the need for more research on this topic.

Although avoidance behavior aims to reduce pain-related fear in the short run, it may paradoxically boost pain-related in the long run, possibly by increasing the *threat value of pain.* People can indeed use their own avoidance behavior to infer threat, i.e. ex-consequentia reasoning[1]:

"I'm avoiding, so it must be painful and/or I must be afraid". In a recent study[41] we provided

support for the bidirectional relationship between fear and avoidance. Using a heat pain paradigm,

participants in the avoidance group were led to believe that they could avoid full exposure to a painful

heat stimulus by pressing the stop button, whereas control group participants believed they were

always exposed to the full painful heat stimulus. In reality, the stimulation was identical in both

groups. During the test without avoidance option, participants in the avoidance group reported higher

levels of pain-related fear. Interestingly, receiving instructions that avoidance was possible already

increased fear, even before avoidance behavior was enacted.

2.5. *Operant learning of pain-related avoidance behavior*

Another mechanism that might contribute to chronic pain disability is *instrumental or operant*

conditioning[39; 43], that is, learning about one's own behavior and its consequences. Successful

avoidance of feared movements (e.g., bending to pick something up with a straight back) can be

negatively reinforced because the feared catastrophe (e.g., spine snapping) does not occur. Despite the

importance of avoidance behavior, a lack of ecologically valid paradigms in humans hampers the

progress in this field. Available paradigms have several limitations including: (1) *instructed*

avoidance precluding the opportunity to study the acquisition of avoidance behavior itself; (2) using

dichotomous responses (press/not press a button) that may lack sensitivity and accuracy; (3) *adaptive*

avoidance is examined: the response effectively cancels the US; (4) using low-cost avoidance (button

press with no response cost). Arguably, this does not reflect the clinical reality well because

especially high-cost avoidance may contribute to disability in the long run. If there is no response cost

to avoidance behavior, the underlying motivation remains elusive as well.

Striving for increased ecological validity, we developed a novel operant pain-related

avoidance paradigm, in which we modeled a response cost of avoidance behavior using a trade-off

between pain probability and effort. In a reaching task, participants moved a robotic arm to a target

location choosing one of three possible trajectories. The shortest/easiest trajectory (T1) was always

paired with pain. If they deviated from this trajectory, pain could be partly or totally prevented

(T2=50% reinforcement; T3=0% reinforcement), but more effort was needed (T2=moderate resistance and deviation; T3=largest resistance and deviation). The yoked control group received the same reinforcement schedule irrespective of their own choice of trajectory. Avoidance behavior was operationalized as the deviation from the shortest/easiest trajectory and results confirmed larger deviations in the experimental group than in the yoked group[24]. Overcoming some limitations of existing methods, this paradigm may hold promise to advance our knowledge about how pain-related avoidance behavior is acquired. It also allows testing for generalization to assess when avoidance behavior becomes maladaptive or excessive.

2.6. Individual differences in fear learning: vulnerability and resilience

The role of vulnerability factors such as pain-related fear, catastrophizing and avoidance have been well-documented in the development and maintenance of chronic pain disability. Far less attention has been dedicated to *resilience factors* such as optimism and positive affect and how these can modulate fear learning and pain-related outcomes[8; 14; 40].

Evidence suggests that positive affect may alter fear learning. First, positive affect may counteract *excessive fear generalization*. Using the voluntary joystick movement paradigm, we showed that experimentally increasing positive affect protected against generalization of fear to safe stimuli[9]. Interestingly, positive affect preserves adaptive fear generalization, but eliminates maladaptive "overgeneralization". Second, positive affect might enhance inhibitory learning[52], the key mechanism underlying exposure treatment. For example, we have shown that trait positive affect protects against deficient safety learning during extinction in individuals with high levels of subclinical anxiety[29]. Positive affect also has been shown to prevent return of fear after successful extinction[51; 53]. Increasing positive affect in chronic pain patients thus may have beneficial effects through limiting excessive spreading of pain-related fear and avoidance as well as through the optimization of (inhibitory) learning processes during treatment[14].

3. **Conclusions**

We reviewed recent developments in fear of movement-related pain and avoidance research, adopting a contemporary learning approach focusing on cognitive, emotional, and behavioral factors, and emphasizing the need for a motivational perspective to further our understanding of the development and persistence of chronic pain disability. Although fear generalization per se is adaptive, we have argued that *excessive generalization* of fear and avoidance may be a pathway to disability. Future research should focus on the bidirectional relationship between fear and avoidance, employ and develop novel ecologically valid methods to study avoidance behavior itself, and the relationship with individual vulnerability factors and resiliencies. Research efforts exploring possible avenues tackling generalization such as positive affect interventions, discrimination training, and neural stimulation techniques may strengthen our treatment repertoire for sufferers from chronic pain.

4. Acknowledgments

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