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Generalization and Extinction of Concept-Based Pain-Related Fear

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Abstract: In chronic pain, pain-related fear seems to overgeneralize to safe stimuli, thus contributing to excessive fear and avoidance behavior. Evidence shows that pain-related fear can be acquired and generalized based on conceptual knowledge. Using a fear conditioning paradigm, we investigated whether this concept-based pain-related fear could also be extinguished. During acquisition, exemplars of 1 action category (conditioned stimuli [CSs]; eg, opening boxes) were followed by pain (CS+), whereas exemplars of another action category were not (CS–; eg, closing boxes). Participants reported more pain-related fear and expectancy toward exemplars of the CS+ category compared with those of the CS– category. During generalization, fear and expectancy spread to novel exemplars (generalization stimuli [GSs]) of the CS+ category (GS+), but not to those of the CS– category (GS–). During extinction, exemplars of both categories were presented in the absence of pain. At the end of extinction, participants no longer reported elevated fear or expectancy toward CS+ exemplars compared to CS– exemplars. These findings were not replicated in either the eye-blink startle or skin conductance measures. This is the first study to demonstrate extinction of concept-based pain-related fear, thus providing evidence for the potential of extinction-based techniques in the treatment of conceptual pain-related fear.

Perspective: This study demonstrates the acquisition, generalization, and extinction of concept-based pain-related fear in healthy participants. These are the first results to show that concept-based pain-related fear can be extinguished, suggesting that conceptual relationships between fear-inducing stimuli may also be important to consider in clinical practice.

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Key words: Pain-related fear, fear conditioning, fear generalization, fear extinction, conceptual generalization, category-learning.

Fear can be acquired through associative learning. The ability to learn that certain stimuli predict aversive outcomes facilitates the employment of appropriate defensive responses. Because threat can present itself in many forms, generalizing a once-learned stimulus–outcome association beyond a specific instance benefits survival. Fear generalization is the adaptive ability to extrapolate information from an aversive learning experience and apply it to novel, similar threatening encounters.^{17,20,24,25}

However, when these defensive responses spread to safe stimuli, fear and avoidance may become maladaptive.^{33–35}

Pain is a strong motivator of fear learning, as it signals bodily threat. For example, Meulders et al³⁸ demonstrated that an initially neutral joystick movement (conditioned stimulus [CS]) came to elicit fear and avoidance (conditioned response) after repeated pairings with a painful electrocutaneous stimulus (unconditioned stimulus [US], pain-US; fear-eliciting CS, CS+), whereas another neutral

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joystick movement (CS−) that was never paired with the pain-US did not.

Fear-avoidance models attribute an important role to pain-related fear in the chronification of acute pain via excessive avoidance behavior.^{9,27,54-56} Chronic pain populations have indeed been shown to overgeneralize pain-related fear to nonthreatening stimuli.³³⁻³⁵ For example, Meulders et al.³⁴ reported that healthy, pain-free controls showed selective fear generalization to novel joystick movements (generalization stimuli [GSs]), similar to the original, painful CS+ joystick movement (GSs+), but not to those resembling the nonpainful CS− movement (GSs−).³⁴ In contrast, fibromyalgia patients demonstrated overgeneralization of pain-related fear to all GSs, suggesting that where healthy individuals demonstrate pain-related fear generalization based on perceptual similarity with the original CS+, people with chronic pain rely less on previous learning and display overgeneralization to all novel stimuli. Furthermore, extinction of fear generalization (ie, repeated exposure to the GS+ in the absence of the pain-US) was slowed down in chronic pain patients,³⁵ suggesting they are less successful in updating their pain-related fear or expectancy beliefs even when disconfirmed.

Fear learning not only occurs based on perceptual stimulus features, humans also possess the ability to generalize conditioned fear based on semantic relationships between stimuli,¹⁵ a process called concept-based fear generalization.¹⁶ Indeed, joystick movements trained to belong to the same category as nonsense words came to evoke pain-related fear, even though only the nonsense words had previously been paired with the pain-US,³ demonstrating the generalization of pain-related fear based on complex semantic relationships between stimuli. Recently, Meulders et al.³⁶ showed that pain-related fear can generalize between functionally equivalent actions. Participants acquired fear to unique exemplars of 1 action category (CS+; eg, opening boxes) and not the other (CS−; eg, closing boxes). Self-reported pain-related fear and expectancy generalized to novel exemplars of the CS+ category (GSs+); the startle eye-blink measure did not corroborate this data pattern.³⁶

Because the original CS+ can be semantically related to many other stimuli that also trigger feared responses, concept-based fear poses additional challenges to the treatment of maladaptive learned fear.^{17,30} However, the extinction of concept-based pain-related fear has not yet been investigated. Therefore, the current study aimed to replicate the acquisition and generalization of conceptual pain-related fear reported by Meulders et al.,³⁶ and to extend those findings by also investigating 1) extinction of concept-based pain-related fear; 2) whether methodological modifications would yield the anticipated differential eye-blink startle responses; and finally, 3) conceptual fear learning in skin conductance,^{15,53} based on previous research reporting. Compared with those of the CS− category during the acquisition and generalization phases, we expected heightened self-report and psychophysiological measures in response to exemplars of the CS+ category and

for this difference to disappear during the extinction phase.

Methods

Participants

Fifty-one pain-free volunteers (17 males; mean $\pm$ standard deviation [SD] age = 31 $\pm$ 16 years, range = 17–70) participated in the current study. The sample size was replicated from the original study by Meulders et al.³⁶ Eighteen participants were psychology students who were recruited using the departmental experiment management system of the KU Leuven and compensated with 1.5 course credits for their participation. The remaining 33 participants were recruited through word of mouth and received no compensation for their participation. Exclusion criteria included pregnancy, heart and cardiovascular disease, respiratory disease (eg, asthma, bronchitis), neurological disease (eg, epilepsy), other severe medical conditions, current or past psychiatric disorders including anxiety disorders and clinical depression, medical advice to avoid stressful situations, presence of electronic medical devices (eg, pacemaker), chronic pain, pain related to the hand or wrist, uncorrected problems of hearing and/or vision, and insufficient knowledge of the Dutch language. All participants completed a health checklist to ensure that none of the exclusion criteria applied before signing the informed consent form. The experimental protocol was approved by the Social and Societal Ethics Committee of the KU Leuven (registration no. G-2015 01 147).

Software and Stimulus Material

The experiment was run on a Windows 8.1 Pro computer (Dell Optiplex 9020; Dell Inc, Dell Way, TX) with 8 GB RAM, an Intel Core i7-4790 CPU processor (Intel, Santa Clara, CA) at 3.60 GHz, and an AMD Radeon R7 250 graphics card (Advanced Micro Devices, Inc, Santa Clara, CA) with 2048 MB of video RAM. Stimulus presentations were controlled using the free software package Affect 4.0.⁴⁹ Visual stimuli were created using the 3-dimensional (3D) graphics software Blender 2.72b (Blender Foundation, Amsterdam, The Netherlands).

CSs consisted of 20 unique exemplars of 2 functional action categories: closing and opening boxes (10 open boxes, 10 closed boxes). To avoid overlap between perceptual features and thus minimize the possibility of irrelevant perceptual features gaining predictive value, mutually exclusive exemplars were used for both action categories, ie, a box with a certain combination of color, shape, and size could only belong to 1 of the 2 action categories. GSs were 16 novel and unique exemplars of the 2 learned action categories (8 open boxes, 8 closed boxes). These GSs were novel and unique in that they had entirely novel and unique combinations of color, shape, and size in comparison to CSs used in the acquisition phase. In this way, it was ensured that the only similarity between CS and GS exemplars was that they belonged to the same action category. Thus, it was

Figure 1. Schematic overview of the experimental task.

investigated whether fear would generalize to novel exemplars that belonged to the CS+ action category, despite perceptual dissimilarities. At the beginning of a trial, a box with its lid either closed or open would appear in the middle of the computer screen. To open or close the box, the participant moved a hydraulic joystick (Paccus Hawk; Paccus Interfaces BV, Almere, The Netherlands) in the signaled direction (ie, left or right). During the participant's movement, an animation was played of the box opening or closing (Fig 1).

The US was a 2-ms painful electrocutaneous stimulation (pain-US) delivered by a commercial constant current stimulator (DS7A; Digitimer, Welwyn Garden City, England). Stimulation was administered through surface Sensormedics electrodes (8 mm) (SensorMedics Corporation, Yorba Linda, CA) filled with water-based lubricating jelly, attached to the wrist of the dominant hand. The intensity of the pain-US was determined individually using a calibration procedure, during which participants received a series of electrocutaneous stimuli

of increasing intensity. They were asked to rate each stimulus on a scale from 0 to 10 (0 = *You feel nothing*; 1 = *You feel something, but it is just a sensation*; 2 = *This sensation is starting to feel unpleasant*; 10 = *This is the worst pain imaginable*). Participants were instructed that we were aiming for a stimulus that was painful and demands some effort to tolerate, corresponding approximately to an 8 on the 0-to-10 pain calibration scale. The mean selected physical stimulus intensity was 27.98 mA (SD 19.52, range = 11–99.9 mA).

Protocol

We used an adapted version of the voluntary joystick movement paradigm³⁶⁻³⁸ to investigate the acquisition, generalization, and extinction of concept-based pain-related fear. The duration of the experiment was ~90 minutes and consisted of different phases: a practice phase, a startle habituation phase, an acquisition phase, a generalization phase, and an extinction phase. Upon

arrival, participants were informed that the experiment involved the repeated presentation of electrocutaneous stimuli (pain-USs) and short loud noises (acoustic startle probes). Furthermore, participants were made aware that at any point during the experiment they were free to decline participation with no negative consequences. Participants then filled in the health checklist and informed consent form, after which electrodes were attached for measuring eyeblink startle and skin conductance responses, as well as electrodes for administering the electrocutaneous stimulation. This was followed by the calibration procedure of the pain-US.

Practice Phase

At the beginning of the practice phase, participants received written instructions about the experimental task on the computer screen. Participants were taught to operate the joystick according to instructions to open and close boxes during 12 trials (6 opening trials, 6 closing trials; 3 right movements per CS category, 3 left movements per CS category; Table 1), to resolve any problems and questions before the actual experiment started. The presentation order was semirandomized with the restriction that a maximum of 2 consecutive trials could consist of exemplars of the same CS category (ie, opening/closing boxes). During this phase, the cursor was visible. In this way, participants were able to continuously track their movements.

Each trial included a pre-CS interval of 6 seconds, after which a box exemplar appeared, accompanied by the direction signal (ie, a red asterisk; Fig 1). This asterisk appeared for 2 seconds on either the left or right end of the screen, and its function was to signal in which direction the participant was required to move the joystick. Subsequently, a white circle appeared in the middle of the computer screen. This white circle informed participants that they were required to move the joystick into its upright starting position. Consequently, participants were taught to correctly position the joystick into this upright position by moving the cursor into the circle. Once the cursor had been successfully moved into the circle, the circle disappeared, and the starting signal (ie, a fixation cross) appeared in the middle of the computer screen to inform participants that they were to move the joystick in the signaled direction.

In the original study by Meulders et al,³⁶ the eyeblink startle measure did not corroborate the heightened responding toward exemplars of the CS+ in comparison to those of the CS−, observed in the self-report measures. Meulders et al³⁶ suggested that this may be the result of “irrelevant” visual stimulus features gaining predictive value and being processed earlier than the “relevant” conceptual information, owing to the salience and priority of visual information in information processing.³⁶ Therefore, to slow down the participants’ movements, the hydraulic joystick was programmed to provide resistive force in the opposite direction of the movement direction required of the participant. (Hydraulic joysticks can be programmed to move independently. This function was used in the current study to provide resistance and slow down participants’ movements. In this way, the hypothesis that concept-based information needs more time to be processed was tested, as the prolonged movement provided participants with more time to process the CS, and to thus display appropriate anticipatory responses.) During the participant’s movement, an animation of the box opening/closing was played. Once the movement was successfully completed, the box disappeared, and after 8 seconds a new trial began. When the participant moved in the wrong direction, an error message appeared, and the trial was restarted. After the disappearance of the direction signal, questions assessing pain-related fear and pain-US expectancy would appear occasionally on the screen, above the box exemplar (3 exemplars from each category; randomly distributed across the 12 trials). To answer these questions, participants used the joystick to move a cursor along a rating scale positioned at the bottom of the box (Fig 1). To confirm their answer, participants clicked a button on the joystick. Thus, participants also practiced answering questions that would be asked during the main experiment. During the practice phase, no startle probes or pain-USs were delivered, and the visibility of the cursor on the screen provided participants with online feedback regarding their left/right movements.

Startle Habituation Phase

Because responses to initial startle probes are often comparatively large, a habituation phase was included

Table 1. Study Design Summary

PRACTICE PHASE (12 TRIALS)	STARTLE HABITUATION PHASE (8 TRIALS)	ACQUISITION PHASE (3 × 20 TRIALS)	GENERALIZATION PHASE (20 TRIALS)	EXTINCTION PHASE (4 × 20 TRIALS)
6 CS+	8 trials	3 × 10 CS+	8 GS+ 8 GS−	4 × 10 CS+
6 CS−		3 × 10 CS−	2 CS+ 2 CS−	4 × 10 CS−

NOTE. CS+ and CS−, respectively, refer to the functional action category that is followed by the pain-US, and the action category that is never followed by the pain-US. GS+ and GS−, respectively, refer to GSs belonging to the CS+ action category and GSs belonging to the CS− category. During the practice phase, the CS+ was not reinforced. During the startle habituation phase, 8 acoustic startle probes were presented (1 per trial). During the acquisition phase, the pain-US was delivered on 80% of CS+ trials, while the CS− was never followed by the pain-US. During generalization, 8 GSs from both functional action categories were presented. Furthermore, to prevent extinction, 2 CSs from both categories were also presented (CS+ 100% reinforcement). During the extinction phase, 10 CSs from both action categories were presented, in the complete absence of the pain-US.

to prevent possible confounding of the data. This phase consisted of 8 trials of 13 seconds, with an intertrial interval (ITI) of 2 seconds. During each trial, a startle probe of 50 ms was delivered between 8 and 12 seconds after trial onset, binaurally through headphones. During this phase, no pain-US was delivered, the computer screen was black, and the lights in the experimental room were dimmed.

Acquisition Phase

The acquisition phase was identical to the practice phase with 3 exceptions. First, there was no longer visual feedback concerning movements (ie, the cursor disappeared upon the appearance of the fixation cross). Second, startle probes were presented on each trial. Third, the pain-US was now delivered according to the experimental contingencies. This phase consisted of 3 blocks of 20 trials (10 CS+ trials, 10 CS– trials; Table 1). During each trial, a unique CS exemplar was presented. Each exemplar belonged only to either the CS+ or CS– category. Thus, there was no overlap between the perceptual features of the exemplars of each action category. As was done in the practice phase, half of the open boxes were to be closed using movements to the left and the other half with movements to the right. Similarly, half of the closed boxes were to be opened with movements to the left and the other half with movements to the right. For each participant 1 of the 2 functional action categories (eg, closing boxes) was designated the CS+; exemplars of this action category were followed by the pain-US on 80% of the trials upon completion of the movement. The other functional category (eg, opening boxes) served as the CS–; exemplars of this category were never followed by the pain-US. Occasionally, after the direction signal disappeared, participants rated prospective pain-related fear and pain-US expectancy, as described in the “Practice Phase” (4 exemplars from each category; randomly distributed across each block).

In the acquisition phase, 1 startle probe was presented on each trial. A startle probe could appear at 1 of 3 time points: before presentation of the CS (pre-CS ITI), during the CS, or after presentation of the CS (post-CS ITI). The duration of the pre-CS ITI was 6 seconds, during which a probe could be presented randomly between 4 and 5.5 seconds after trial onset. The during-CS probe would appear 500 ms after successful placement of the joystick in its upright position, as described above. The duration of the post-CS ITI period was 8 seconds, during which the probe could appear randomly at any time between 2.5 and 4.5 seconds after post-CS ITI onset. Participants were not explicitly informed about CS–US contingencies but were instructed to pay attention to when the pain-US appeared.

Generalization Phase

The generalization phase was comparable to the acquisition phase with some exceptions. This phase consisted of 8 novel and unique exemplars of both the CS+ and CS– categories, referred to as generalization stimuli

(GSs+ and GSs–, respectively; 16 novel exemplars in total), which were tested during 1 block of 20 trials (Table 1). Furthermore, these GSs were never followed by the pain-US. Consequently, it was investigated whether fear would generalize to exemplars that looked dissimilar from the ones encountered in the acquisition phase, and thus had never been paired with pain yet belonged to the same action category. To prevent extinction during the generalization phase, 2 original CS+ and CS– exemplars used in the acquisition phase were presented as well (2 of each CS category, CS+ exemplars 100% reinforced). During the generalization phase, prospective pain-related fear and pain-US expectancy ratings were presented on each trial. In the generalization phase, startle probes were delivered only during CSs according to the timing described above.

Extinction Phase

During the extinction phase, the original CS+ and CS– exemplars used in the acquisition phase were presented again. However, none of these original exemplars were followed by the pain-US. The extinction phase consisted of 4 blocks of 20 trials (10 original CS+ exemplars, 10 original CS– exemplars; Table 1). Except for the change in CS+ reinforcement, the extinction phase was identical to the acquisition phase, including timing and frequency of startle probes and prospective fear and US-expectancy ratings.

Main Outcome Measures

Prospective Fear of Movement-Related Pain Ratings

During all phases of the experiment, participants provided prospective pain-related fear ratings (*To what extent are you afraid to perform this action?*). Participants rated how afraid they were to perform the upcoming movement before doing so (after presentation of the direction signal and before presentation of the white circle). They were instructed to answer this question by using the joystick to move the cursor along an 11-point Likert scale ranging from 0 = “Not afraid at all” to 10 = “Very afraid” and clicking to confirm.

Prospective Pain-US Expectancy Ratings

During all phases of the experiment, participants provided prospective pain-US expectancy ratings (*To what extent do you expect an electrocutaneous stimulus after this action?*), again, before performing the signaled movement. They were instructed to answer these questions by using the joystick to move the cursor along an 11-point Likert scale ranging from 0 = “Not at all” to 10 = “Very much” and clicking to confirm.

Eye-Blink Startle Modulation

The eye-blink startle response is a reflexive cross-species reaction to startle-evoking stimuli (such as acoustic

startle probes, ie, sudden loud noises), which can be measured by the tension in the muscles underneath the eye.^{4,12} Startle modulation, which refers to potentiation of the startle reflex during states of aversive anticipation, is a widely accepted proxy of conditioned fear.^{23,26} Eye-blink startle responses were measured using 3 Ag/AgCl SensorMedics electrodes (4 mm) SensorMedics Corporation, Yorba Linda, CA filled with microlyte gel. Two of these electrodes were placed under the left eye to measure electromyographic (EMG) activity and 1 on the forehead to act as a ground electrode.⁴ The startle probe was a 50-ms-long 100-dBA burst of white noise with instantaneous rise time, presented binaurally through headphones. The raw signal was amplified using a Coulbourn isolated bioamplifier (Coulbourn Instruments, Whitehall, PA) with bandpass filter (LabLinc v75-04). The recording bandwidth of the signal was between 90 and 500 Hz (~3 dB). The signal was rectified online and smoothed by a Coulbourn multifunction integrator (LabLinc v76-23 A) with a time constant of 20 ms. The EMG signal was digitized at 1,000 Hz from 500 ms before the onset of the auditory startle probe until 1,000 ms after probe onset (see Muelers et al³⁷). Eyeblink startle responses during the CS/GS movement were taken as an index of cued pain-related fear, whereas responses during the ITI were taken as an index of contextual pain-related fear.

Skin Conductance Response

Skin conductance response (SCR) relies on increased eccrine gland (sweat glands found on the palms of the hands and soles of the feet) activity resulting from arousal.⁴⁷ Because fear increases arousal levels, elevated skin conductance is widely used as a proxy of conditioned fear.¹⁹ Skin conductance was measured using 2 Biopac EL507 EDA disposable snap electrodes (Biopac Systems Inc, Galeta, CA) placed on the palm of the non-dominant hand, which participants were asked to hold as still as possible throughout the course of the experiment. A Coulbourn isolated skin conductance coupler (LabLinc v71-23) provided a constant 0.5 V across all electrodes. The signal was digitized at 100 Hz.

Manipulation Checks

Retrospective Pain-Related Fear

As a manipulation check, after each experimental block, participants were asked to rate how fearful they were of the functional CS categories (opening vs closing boxes). To assess this, participants answered the question *To what extent were you afraid to perform the action of opening/closing a box during the previous block?* on a Likert scale ranging from 0 = "Not afraid at all" to 10 = "Very afraid." To ensure that this assessment would not focus participants' attention solely on the functional action categories that were of relevance to predict the pain, and thus make the CS-US contingency too obvious, they also rated fear related to other perceptual and proprioceptive features that varied among

the different exemplars of the functional categories but were not relevant to predict pain: a) movement direction, b) size, and c) color. Participants responded to the following questions on a Likert scale ranging from 0 = "Not afraid at all" to 10 = "Very afraid": *To what extent were you afraid to move to the left/right during the previous block?*; *To what extent were you afraid of dark/light colored boxes during the previous block?*; and *To what extent were you afraid of big/small boxes during the previous block?*

Retrospective Pain Intensity and Unpleasantness

To monitor possible habituation and sensitization effects, participants responded to the questions *How painful did you find the electrocutaneous stimulus during the previous block?* and *How unpleasant did you find the electrocutaneous stimulus during the previous block?* on a Likert scale ranging from 0 = "Not painful/unpleasant at all" to 10 = "Very painful/unpleasant." These questions were also asked after each experimental block.

Postexperimental Questionnaires

After completion of the experiment, participants filled out questionnaires assessing various psychological trait variables. The questionnaires used here were the Fear of Pain Questionnaire,^{31,45} the Pain Catastrophizing Scale,⁵⁰ the Positive and Negative Affect Schedule,^{18,57} and the trait portion of the State-Trait Anxiety Inventory.^{48,51} These questionnaires were included for meta-analytical reasons and therefore are not reported in this article.

Experimental Setting

Participants were seated in an armchair in the experimental room, in front of a computer screen with the joystick within reach. The experimenter was seated in an adjacent control room throughout the duration of the experiment. Participants and their physiological responses (startle eyeblink and SCR) were observed online by the experimenter, via a closed-circuit TV installation and computer monitors, respectively. Communication between the participant and experimenter was possible through an intercom system.

Response Definition and Data Analysis Overview

Response Definition of the Startle Response

Peak startle amplitudes, defined as the maximum of the response curve within 21 to 175 ms after the startle probe onset, were calculated using the modular script-based program Psychophysiological Analysis.¹³ All startle waveforms were visually inspected offline, and technical abnormalities and artifacts were eliminated. All peak amplitudes were scored by subtracting their

baseline scores (averaged EMG level between 1 and 20 ms after startle probe onset). To account for interindividual differences in physiological responsiveness, raw scores were transformed into z-scores. T-scores were used in the figures to optimize visualization and avoid negative values on the y-axis.

Response Definition of the SCR

Skin conductance was measured continuously during the experiment. Only participants who showed detectable skin responses were included in the SCR analyses. One participant was excluded for this reason. To avoid response artifacts from the pain-US, statistical analyses were performed on the average SCR for the trials in which no pain-US was delivered. Skin conductance was analyzed offline with a Matlab software script (The Math Works Inc., Natick, MA). Response amplitudes (μ Siemens) were calculated per trial whereby the maximum value is subtracted from a preceding lower value (ie, baseline) in the time window of the movement. To account for interindividual differences, z-transformations were carried out on each raw SCR and then converted to t-scores. All trials in which pain-US or fear of pain and pain-expectancy questions appeared were excluded from the SCR analysis, to minimize possible confounds. This meant that 87% of CS+ trials and 40% of CS− trials in the acquisition phase were excluded from the SCR analysis.

Data Analysis Overview

Paired-sample t-tests were run on practice phase data, and separate repeated-measures (RM) analyses of variance (ANOVAs) were carried out on the respective dependent measures to examine the acquisition, generalization, and extinction of pain-related fear based on conceptual knowledge. The α level was set at .05. Bonferroni corrections were applied in case of multiple planned comparisons. Greenhouse–Geisser corrections are reported when appropriate. Uncorrected degrees of freedom and corrected P values are reported together with ε , and the indication of effect size η_p^2 is reported for significant ANOVA effects and Cohen's d for planned comparisons. All statistical analyses were run on Statistica 13.1 software (StatSoft, Inc, Tulsa, OK).

Results

Manipulation Checks

Retrospective Pain-Related Fear Ratings

To ensure that the relevant features (closing/opening boxes) of the CS exemplars elicited more fear than irrelevant features (direction of movement, color, shape, and size of the boxes), an 8×8 (Feature [CS+, CS−, left, right, dark, light, small, large] $\times$ Block [acquisition (ACQ1–3), generalization (GEN), extinction (EXT1–4)]) RM ANOVA was conducted. This analysis yielded a significant main effect of Feature, $F_{7,350} = 11.56$, $P < .001$, $\varepsilon = .47$, $\eta_p^2 = .19$,

and Block, $F_{7,350} = 47.37$, $P < .001$, $\varepsilon = .48$, $\eta_p^2 = .49$, both of which were qualified by a significant interaction effect, $F_{49,2450} = 3.38$, $P < .001$, $\varepsilon = .28$, $\eta_p^2 = .06$. Planned comparisons confirmed that pain-related fear ratings for exemplars of the CS+ category were higher than for those of the CS− category during the last acquisition block, $F_{1,50} = 44.13$, $P < .001$, $d = 1.88$. This was also the case during the generalization phase, $F_{1,50} = 33.54$, $P < .001$, $d = 1.64$. By the end of the extinction phase (EXT4), this difference was no longer significant, $F_{1,50} = 1.54$, $P = .220$, $d = .35$. Further comparisons revealed a significant difference between fear ratings for CS+ exemplars and irrelevant stimulus features in both the last acquisition block, $F_{1,50} = 21.18$, $P < .001$, $d = 1.30$, and the generalization phase, $F_{1,50} = 19.55$, $P < .001$, $d = 1.25$. This difference was no longer significant during the final extinction block, $F_{1,50} = 2.31$, $P = .13$. Furthermore, fear ratings for exemplars of the CS− category were significantly lower than fear ratings in response to irrelevant stimulus features in the last acquisition block, $F_{1,50} = 39.62$, $P < .001$, $d = 1.78$, and generalization phase, $F_{1,50} = 32.11$, $P < .001$, $d = 1.60$. In the last extinction block, this difference was no longer significant, $F_{1,50} = .9$, $P = .35$ (Fig 2).

Retrospective Pain Intensity and Unpleasantness Ratings

A 2×4 (Rating [intensity, unpleasantness] $\times$ Block [ACQ1–3, GEN]) RM ANOVA conducted on retrospective pain intensity and pain unpleasantness ratings showed a significant main effect of Rating, $F_{1,50} = 40.57$, $P < .001$, $\eta_p^2 = .45$, but not of Block, $F_{1,50} = 1.27$, $P = .287$, $\eta_p^2 = .025$. Furthermore, no significant interaction effect was found between Rating and Block, $F_{7,350} = 1.38$, $P = .253$, $\eta_p^2 = .027$ (Fig 3).

Prospective Fear of Movement-Related Pain Ratings

Practice

Paired-sample t-tests were conducted on the mean prospective pain-related fear ratings for the CS+ and CS− categories during the practice phase. This analysis revealed no significant differences in fear elicited by the exemplars of the CS+ category and those of the CS− category during the practice phase, $t_{50} = 1.587$, $P = .199$, thus confirming the absence of baseline differences in fear responding between the CS categories.

Acquisition

A 2×3 (Stimulus Category [CS+, CS−] $\times$ Block [ACQ1–3]) RM ANOVA was carried out on the mean pain-related fear ratings for the CS categories during the 3 acquisition blocks. There was a significant main effect of Stimulus Category, $F_{1,50} = 24.89$, $P < .001$, $\eta_p^2 = .33$, and a significant main effect of Block, $F_{2,100} = 4.22$, $P = .029$, $\varepsilon = .73$, $\eta_p^2 = .08$. These were qualified by a significant Stimulus Category $\times$ Block interaction, $F_{2,100} = 12.82$, $P < .001$, $\varepsilon = .98$, $\eta_p^2 = .20$,

Figure 2. Mean ratings of retrospective fear of movement-related pain. Mean ratings of retrospective fear of movement-related pain in response to the CS+/CS−, direction of the joystick movement (right/left), and color and size of the box exemplars during acquisition (ACQ1–3), generalization (GEN), and extinction (EXT1–4). Error bars represent 95% confidence intervals.

Figure 3. Mean ratings of retrospective pain-US intensity and unpleasantness. Mean ratings of retrospective pain-US intensity and unpleasantness during the acquisition (ACQ1–3) and generalization (GEN) phases. Error bars represent 95% confidence intervals.

Figure 4. Mean prospective self-reported fear of movement-related pain. Mean prospective self-reported fear of movement-related pain in response to the CS+/CS− exemplars during practice (P), acquisition (ACQ1–3), and extinction (EXT1–4) and in response to the GS+/GS−/CS+/CS− exemplars during generalization (GEN). Error bars represent 95% confidence intervals.

suggesting that fear toward the respective CS category was acquired over time. Planned comparisons confirmed that although there was no significant difference in the first acquisition block ($F_{1,50} = 3.19$, $P = .080$, $d = .5$), exemplars of the CS+ category elicited more pain-related fear than did those of the CS− category in the second acquisition block ($F_{1,50} = 20.78$, $P < .001$, $d = 1.29$). This differential effect remained significant in the third acquisition block ($F_{1,50} = 23.41$, $P < .001$, $d = 1.37$) (Fig 4).

Generalization

To investigate generalization of pain-related fear to the novel exemplars (GSs) of the learned CS categories, an RM ANOVA with Stimulus Category (GS+, GS−, CS+, CS−) as a within-subject variable was conducted on prospective fear ratings during the generalization phase. This analysis yielded a significant main effect of Stimulus Category, $F_{3,150} = 19.07$, $P < .001$, $\varepsilon = .53$, $\eta_p^2 = .28$. Planned comparisons confirmed that the original exemplars of the CS+ category continued to elicit more pain-related fear than did those of the CS− category, $F_{1,20} = 19.37$, $P < .001$, $d = 1.25$, suggesting that no fear extinction occurred during the generalization test. Furthermore, in line with our hypothesis, participants reported more pain-related fear in response to novel exemplars of the CS+ category (GS+) compared with those of the CS− category (GS−), $F_{1,50} = 23.31$, $P < .001$, $d = 1.37$. No such differences occurred between the CS+ and GS+ exemplars, $F_{1,50} = .06$, $P = .808$, $d = .07$. In contrast, fear ratings for the CS− and GS− seemed to differ, $F_{1,50} = 5.48$, $P = .023$, $d = .66$. However, after the

Bonferroni correction, this difference was no longer significant ($P > .008$). These findings suggest that learned contingencies based on a specific set of exemplars transferred to novel exemplars of a conceptually similar category. Furthermore, the lack of significant differences between original and novel CS exemplars suggests that there is no generalization decrement (Fig 4).

Extinction

A 2×5 (Stimulus Category [CS+, CS−] $\times$ Block [ACQ3, EXT1–4]) RM ANOVA was carried out on the mean prospective pain-related fear ratings during the extinction phase. There was a significant main effect of Stimulus Category, $F_{1,50} = 25.83$, $P < .001$, $\eta_p^2 = .34$, and Block, $F_{4,200} = 32.99$, $P < .001$, $\varepsilon = .46$, $\eta_p^2 = .40$. This was qualified by a significant Stimulus Category $\times$ Block interaction effect, $F_{4,200} = 10.51$, $P < .001$, $\varepsilon = .62$, $\eta_p^2 = .17$. Planned comparisons confirmed that the significant difference between fear ratings for the CS+ and CS−, evident in the last acquisition block, remained as such during the first extinction block, $F_{1,50} = 4.55$, $P = .038$, $d = .60$. In the last extinction block, this difference was no longer significant, $F_{1,50} = 1.93$, $P = .171$, $d = 1.01$, suggesting successful extinction of differential category-based pain-related fear (Fig 4).

Prospective Pain-US Expectancy Ratings

The prospective pain-US expectancy ratings showed the same data pattern as the prospective fear of movement-related pain ratings. Because of the high correlation between the 2 ratings and for the sake of brevity,

Figure 5. Mean startle eyeblink amplitudes. Mean startle eyeblink amplitudes during the CS+/CS− exemplars in the acquisition (ACQ1–3), generalization (GEN) and extinction (EXT1–4) phases, and during the ITI in the acquisition and extinction phases. Error bars represent 95% confidence intervals.

we do not include a detailed report of the results in our study. The complete results of the RM ANOVA and planned contrasts for these ratings, as well as the results of the Spearman's ρ correlational analyses between pain-related fear and US-expectancy, are available as [online supplementary material](#).

Eyeblink Startle Modulation

Acquisition

A 3×3 (Stimulus Type [CS+, CS−, ITI] $\times$ Block [ACQ1–3]) RM ANOVA was conducted on the mean startle amplitudes during probes presented during exemplars of the CS+ and CS− categories, and during the ITI probes in the acquisition phase. There was a significant main effect of Stimulus Type, $F_{2,100} = 14.65$, $P < .001$, $\varepsilon = .80$, $\eta_p^2 = .23$, and Block, $F_{2,100} = 11.33$, $P < .001$, $\varepsilon = .87$, $\eta_p^2 = .19$, both of which were qualified by a significant Stimulus Type $\times$ Block interaction, $F_{4,200} = 3.60$, $P = .011$, $\varepsilon = .87$, $\eta_p^2 = .07$. Planned comparisons, however, revealed no significant difference in startle amplitudes in response to the presentation of a CS+ category exemplar, compared to the presentation of a CS− category exemplar during the first, $F_{1,50} = .33$, $P = .568$, $d = .16$, or the last, $F_{1,50} = .04$, $P = .837$, $d = .06$, acquisition block. However startle amplitudes during both CS categories were significantly higher than during the ITI in the first, $F_{1,50} = 5.95$, $P < .05$, $d = .69$, and last, $F_{1,50} = 20.64$, $P < .001$, $d = 1.28$, acquisition blocks, suggesting elevated psychophysiological

arousal during both CS categories in comparison with responses to the (safe) context alone. Because of the lack of differential acquisition effect in the eyeblink startle responses, we do not further report the generalization and differential extinction effects (Fig 5).

SCR

Acquisition

A 2×1 (Stimulus Type [CS+, CS−] $\times$ Phase [ACQ/EXT]) RM ANOVA on the SCRs revealed a significant main effect of Phase, $F_{1,49} = 4.44$, $P < .05$. There was no significant main effect of Stimulus Type, $F_{1,49} = .16$, $P = .69$, or interaction effect, $F_{1,49} = 1.23$, $P = .27$. The SCRs for CS+ and CS− exemplars decreased from the acquisition phase to the extinction phase (Fig. 6). Because of the lack of differential acquisition effect in the SCRs, we did not further test or report the generalization and differential extinction effects.

Discussion

Humans can acquire fear based on conceptual knowledge. The aim of the current study was to replicate the previously demonstrated³⁶ acquisition and generalization of concept-based pain-related fear and investigate whether such fear could subsequently be extinguished. An additional aim was to investigate whether

Figure 6. Mean skin conductance amplitudes. Mean skin conductance amplitudes during the CS+/CS– exemplars during acquisition (ACQ1–3) and extinction (EXT1–4), and in response to the GS+/GS– exemplars during generalization (GEN). Error bars represent 95% confidence intervals.

methodological modifications—ie, 1) slowing down participants' joystick movements and 2) measuring SCRs—would abolish the previously reported dissociation between self-report and psychophysiological measures of concept-based pain-related fear.³⁶

First, we successfully replicated the acquisition of fear of movement-related pain based on superordinate action category membership. In contrast, neither eye-blink startle responses nor SCRs were elevated in response to the CS+ category compared with the CS– category. However, in line with the original study by Meulders et al,³⁶ exemplars of both CS categories elicited higher startle responses than the context alone (ie, ITI startle responses), again suggesting elevated but nondifferential fear toward both CS categories compared with the context. Additionally, both psychophysiological measures decreased from the acquisition phase to the extinction phase, suggesting a decrease in fear. Second, we replicated the spreading of category-based fear to novel exemplars of the learned CS+ category (GSs+) but not to novel exemplars of the CS– category (GSs–). Third, we demonstrated that pain-related fear that is acquired based on conceptual knowledge about stimulus category membership can also be extinguished. Specifically, participants no longer reported elevated pain-related fear or pain-US expectancy for exemplars of the CS+ category, compared to those of the CS– category, after repeated

presentations of the original CS+ exemplars without painful stimulation.

Despite methodological adaptations, the heightened fear and expectancy ratings in response to exemplars of the CS+ category compared with the CS– category were not observed in our psychophysiological measures. These results correspond to those previously reported by Meulders et al,³⁶ who suggested that the nondifferential startle responses between CS categories resulted from irrelevant stimulus features (movement direction, size and color of boxes) acquiring predictive value and generating a certain level of fear. The authors further proposed that processing category-based information is a demanding task that may require more time and effort to complete. In the current study, these possibilities were controlled for by minimizing overlap between perceptual stimulus features by using category-specific exemplars, and by slowing down participants' joystick movements, respectively. However, because of its salience, visual information is often processed faster than other information.^{21,43} Therefore, the processing of these irrelevant perceptual stimulus features may have preceded the processing of the relevant conceptual information and thus produced potentiated startle responses that were independent of the effect of interest, despite giving participants more time to process the category-specific information. Furthermore, because joystick movements in 1 direction were partially

reinforced (ie, half of the movements to the right/left were followed by pain), movement directions may have produced a level of fearful responding. In line with this, irrelevant stimulus features generated fear reports in between the CS+ and CS− categories, suggesting that these features indeed elicited fearful responding to some extent (Fig. 2). However, given that 2 previous studies using the eye-blink startle response as a measure of concept-based fear reported similar effects, it remains feasible that the absence of the differential startle effect is a genuine finding.^{32,36}

The current results are in contrast with previous research reporting observable concept-based learning in SCRs. Dunsmoor et al¹⁵ showed elevated SCRs and pain expectancy ratings in response to exemplars of a superordinate category paired with a painful shock (eg, pictures of animals) compared with exemplars of another superordinate category not paired with shock (eg, pictures of tools). Vervoort et al⁵³ reported heightened SCRs in response to a CS+, and these generalized to other members of the learned CS+ category. Our study differs from those of Dunsmoor et al¹⁵ and Vervoort et al⁵³ in some features. Specifically, the previous studies used purely visual stimuli with controlled CS durations (6 s), whereas the current paradigm employed stimuli of mixed modalities (visual-proprioceptive). Because of the proprioceptive nature of our stimuli, CS duration was dependent on the participants' movement speed (1–1.5 s), which was significantly shorter than the duration of visual CSs in previous studies (6 s). Because the SCR is a long-latency response that takes time to start and peak (the response typically starts 1–4 s after stimulus presentation and peaks 0.5–5 s later),^{5,29} the short joystick movements did not allow enough time between the CS+ and the pain-US presentation to disentangle conditioned and unconditioned SCRs. For that reason, data from reinforced trials were excluded from the analysis. Thus, an explanation for the lack of differential SCR results may lie in the very limited number of trials included in our analysis.

Our results correspond to those of Meulders et al,³⁶ who demonstrated that pain-related fear can be acquired and generalized based on conceptual knowledge about category membership. Furthermore, our results extend the original findings by providing evidence that such conceptual pain-related fear can also be extinguished. Extinction learning is the mechanism underlying exposure-based treatments, which are widely used to reduce maladaptive fear^{14,22,44} and, specifically, chronic pain conditions.^{2,41,28} However, to our knowledge, the applicability of extinction techniques to concept-based pain-related fear have never been studied before. Fear acquisition was found to be delayed in the original³⁶ and current studies, compared with previous studies investigating fear of movement-related pain using the voluntary joystick movement paradigm.³⁹ Given that multiple CS exemplars are paired with the pain-US during concept-based fear acquisition, participants need to sort out which features of the CS are most relevant (eg, color, shape, or action category) in predicting the pain-US. Thus, more time may be required to extract the category-information and successfully inhibit responses

to perceptual information. Furthermore, given that extinction learning is considered to represent learning an exception to a rule,⁷ and all CS exemplars in concept-based fear learning are unique, it may take longer to generalize that rule. In this regard, Vervoort et al⁵³ found that extinction of concept-based learning to the original CS+ spreads to conceptually related GSs, but not the other way around,⁵³ suggesting that successful extinction of a concept-based GS may also represent learning an exception to the category-rule that does not generalize back to all members of the same category.

Fear extinction is more context specific than fear acquisition^{6–8} and thus generalizes less readily to stimuli or contexts that were not present during initial fear acquisition.^{7,10,46,52} Because the original CS+ is not always attainable, successful extinction of concept-based fear may require the application of additional learning steps, such as translating the predictive value of an extinguished exemplar (GS) back to its broader category (CS+). Various strategies have been found to enhance fear extinction.⁴² For instance, the use of more than 1 fear-eliciting stimulus predicting the same aversive outcome has been found to attenuate the return of fear,¹¹ suggesting that using multiple conceptually related fear-inducing stimuli may facilitate the translation of conceptually related GSs to their broader CS+ category.

Some limitations should be addressed. First, a sample of mainly young, healthy, pain-free adults was used in the current study. Given that differences in learning mechanisms may exist between healthy and clinical participants,^{33,35} validation of the current results in patient populations is necessary. Second, despite methodological modifications, our main findings in self-reported fear and pain expectancy were replicated in neither of our psychophysiological measures. It has been suggested that the eye-blink startle response is not always sufficiently sensitive to detect subtle differences in the modulation between multiple stimuli in ambiguous and complex experimental designs,¹ such as those of the original and current studies. Therefore, the eye-blink startle response simply may have not been the ideal psychophysiological measure of fear for the current study. Furthermore, although pain-related fear ratings tend to be quite low compared with expectancy measures,⁴⁰ those of the current study were particularly low, which may also partially explain the lack of differential eye-blink startle effects. Third, a large amount of SCR data was excluded from trials in which the pain-US or fear and expectancy questions were presented, meaning the SCR analysis had relatively low statistical power. More SCR data may have produced different results; however, this was not possible using the current setup.

The current results corroborate the potential role of conceptual knowledge in the acquisition and generalization of pain-related fear. They also provide evidence for the applicability of extinction procedures to reduce concept-based pain-related fear. This is especially consequential given that during treatment, the way in which fear is extinguished will depend on the type of fear that was acquired (eg, perceptual or conceptual). Because fear may originally be acquired based on conceptual

information, it may prove more useful to identify and target fear beliefs toward the conceptual category rather than the perceptual stimulus features, which are also present but are not relevant in triggering fear. However, empirical demonstrations of whether concept-based pain-related fear can be extinguished are scarce. Future research should aim to replicate the current study in clinical samples for reliable generalization of the findings to chronic pain populations.

References

1. Ahmed O, Lovibond PF: The impact of previously learned feature-relevance on generalisation of conditioned fear in humans. *J Behav Ther Exp Psychiatry* 46:59-65, 2015
2. Bailey KM, Carleton RN, Vlaeyen JWS, Asmundson GJG: Treatments addressing pain-related fear and anxiety in patients with chronic musculoskeletal pain: A preliminary review. *Cogn Behav Ther* 39:46-63, 2010
3. Bennett MP, Meulders A, Baeyens F, Vlaeyen JW: Words putting pain in motion: The generalization of pain-related fear within an artificial stimulus category. *Front Psychol* 6:520, 2015
4. Blumenthal TD, Cuthbert BN, Filion DL, Hackley S, Lipp OV, Van Boxtel A: Committee report: Guidelines for human startle eyeblink electromyographic studies. *Psychophysiology* 42:1-15, 2005
5. Boucsein W, Fowles DC, Grimnes S, Ben-Shakhar G, Roth WT, Dawson ME, Filion DL: Publication recommendations for electrodermal measurements. *Psychophysiology* 49:1017-1034, 2012
6. Bouton ME: Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. *Biol Psychiatry* 52:976-986, 2002
7. Bouton ME: Context and behavioral processes in extinction. *Learning Memory* 11:485-494, 2004
8. Bouton ME, Woods AM, Moody EW, Sunsay C, García-Gutiérrez A: Counteracting the context-dependence of extinction: relapse and tests of some relapse prevention methods. Craske MG, Hermans D, Vansteenwegen D (eds.), *Fear and Learning: From Basic Processes to Clinical Implications*. Washington, DC: American Psychological Association, 2006, pp 175-196
9. Crombez G, Eccleston C, Van Damme S, Vlaeyen JW, Karoly P: Fear-avoidance model of chronic pain: The next generation. *Clin J Pain* 28:475-483, 2012
10. Culver NC, Stoyanova M, Craske MG: Clinical relevance of retrieval cues for attenuating context renewal of fear. *J Anxiety Disord* 25:284-292, 2011
11. Culver NC, Vervliet B, Craske MG: Compound extinction: using the Rescorla–Wagner model to maximize exposure therapy effects for anxiety disorders. *Clin Psychol Sci* 3:335-348, 2015.
12. Davis M, Walker DL, Miles L, Grillon C: Phasic vs sustained fear in rats and humans: Role of the extended amygdala in fear vs anxiety. *Neuropsychopharmacology* 35:105-135, 2010

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Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jpain.2018.09.010>.

13. de Clercq A, Verschuere B, de Vlieger P, Crombez G: Psychophysiological analysis (PSPHA): A modular script-based program for analyzing psychophysiological data. *Behav Res Methods* 38:504-510, 2006
14. Deacon BJ, Abramowitz JS: Cognitive and behavioral treatments for anxiety disorders: A review of meta-analytic findings. *J Clin Psychol* 60:429-441, 2004
15. Dunsmoor JE, Martin A, LaBar KS: Role of conceptual knowledge in learning and retention of conditioned fear. *Biol Psychol* 89:300-305, 2012
16. Dunsmoor JE, Murphy GL: Categories, concepts, and conditioning: How humans generalize fear. *Trends Cogn Sci* 19:73-77, 2015
17. Dymond S, Dunsmoor JE, Vervliet B, Roche B, Hermans D: Fear generalization in humans: Systematic review and implications for anxiety disorder research. *Behav Ther* 46:561-582, 2015
18. Engelen U, De Peuter S, Victor A, Diest I, Van den Bergh O: [Further validation of the Positive and Negative Affect Schedule (PANAS) and comparison of two Dutch versions]. *Gedrag Gezondheid*, 34:89-102, 2006
19. Esteves F, Parra C, Dimberg U, Öhman A: Nonconscious associative learning: Pavlovian conditioning of skin conductance responses to masked fear-relevant facial stimuli. *Psychophysiology* 31:375-385, 1994
20. Ghirlanda S, Enquist M: A century of generalization. *Animal Behav* 66:15-36, 2003
21. Gibson JJ: Adaptation, after-effect and contrast in the perception of curved lines. *J Exp Psychol* 16:1, 1933
22. Gould RA, Otto MW, Pollack MH, Yap L: Cognitive behavioral and pharmacological treatment of generalized anxiety disorder: A preliminary meta-analysis. *Behav Ther* 28:285-305, 1997
23. Grillon C: Startle reactivity and anxiety disorders: Aversive conditioning, context, and neurobiology. *Biol Psychiatry* 52:958-975, 2002
24. Honig WK, Urcioli PJ: The legacy of Guttman and Kalish (1956): Twenty-five years of research on stimulus generalization. *J Exp Anal Behav* 36:405-445, 1981
25. Kalish HI: Stimulus generalization. In: Marx MH, (ed): *Learning: Processes*. Oxford, UK, Macmillan Oxford, 1969:207-297
26. Lang PJ, Davis M, Öhman A: Fear and anxiety: Animal models and human cognitive psychophysiology. *J Affect Disord* 61:137-159, 2000

27. Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW: The fear-avoidance model of musculoskeletal pain: Current state of scientific evidence. *J Behav Med* 30:77-94, 2007
28. Leonhardt C, Kuss K, Becker A, Basler H-D, de Jong J, Flatau B, Laekeman M, Mattenklodt P, Schuler M, Vlaeyen J: Graded exposure for chronic low back pain in older adults: A pilot study. *J Geriatr Phys Ther* 40:51-59, 2017
29. Lonsdorf TB, Menz MM, Andreatta M, Fullana MA, Golkar A, Haaker J, Heitland I, Hermann A, Kuhn M, Kruse O, Meir Drexler S, Meulders A, Nees F, Pittig A, Richter J, Romer S, Shibani Y, Schmitz A, Straube B, Vervliet B, Wendt J, Baas JMP, Merz CJ: Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. *Neurosci Biobehav Rev* 77:247-285, 2017
30. Marks IM: *Fears, Phobias, and Rituals: Panic, Anxiety, and Their Disorders*. Oxford, UK, Oxford University Press on Demand, 1987
31. McNeil DW, Rainwater 3rd AJ: Development of the Fear of Pain Questionnaire—III. *J Behav Med* 21:389-410, 1998
32. Meulders A, Bennett MP: The concept of contexts in pain: Generalization of contextual pain-related fear within a de novo category of unique contexts. *J Pain* 19:76-87, 2018
33. Meulders A, Harvie DS, Bowering JK, Caragianis S, Vlaeyen JW, Moseley GL: Contingency learning deficits and generalization in chronic unilateral hand pain patients. *J Pain* 15:1046-1056, 2014.
34. Meulders A, Jans A, Vlaeyen JW: Differences in pain-related fear acquisition and generalization: An experimental study comparing patients with fibromyalgia and healthy controls. *Pain* 156:108-122, 2015
35. Meulders A, Meulders M, Stouten I, De Bie J, Vlaeyen JW: Extinction of fear generalization: A comparison between fibromyalgia patients and healthy control participants. *J Pain* 18:79-95, 2017.
36. Meulders A, Vandaal K, Vlaeyen JW: Generalization of pain-related fear based on conceptual knowledge. *Behav Ther* 48:295-310, 2017
37. Meulders A, Vandebroek N, Vervliet B, Vlaeyen JWS: Generalization gradients in cued and contextual pain-related fear: An experimental study in healthy participants. *Front Hum Neurosci* 7:345, 2013
38. Meulders A, Vansteenwegen D, Vlaeyen JW: The acquisition of fear of movement-related pain and associative learning: A novel pain-relevant human fear conditioning paradigm. *Pain* 152:2460-2469, 2011
39. Meulders A, Vlaeyen JW: Reduction of fear of movement-related pain and pain-related anxiety: An associative learning approach using a voluntary movement paradigm. *Pain* 153:1504-1513, 2012
40. Meulders A, Vlaeyen JWS: The acquisition and generalization of cued and contextual pain-related fear: An experimental study using a voluntary movement paradigm. *Pain* 154:272-282, 2013
41. Nicholas M, Asghari A, Sharpe L, Brnabic A, Wood B, Overton S, Tonkin L, Sousa M, Finniss D, Beeston L: Cognitive exposure versus avoidance in patients with chronic pain: Adherence matters. *Eur J Pain* 18:424-437, 2014
42. Pittig A, van den Berg L, Vervliet B: The key role of extinction learning in anxiety disorders: Behavioral strategies to enhance exposure-based treatments. *Curr Opin Psychiatry* 29:39-47, 2016
43. Posner MI, Nissen MJ, Klein RM: Visual dominance: An information-processing account of its origins and significance. *Psychol Rev* 83:157-171, 1976
44. Powers MB, Halpern JM, Ferenschak MP, Gillihan SJ, Foa EB: A meta-analytic review of prolonged exposure for post-traumatic stress disorder. *Clin Psychol Rev* 30:635-641, 2010
45. Roelofs J, Peters ML, Deutz J, Spijker C, Vlaeyen JW: The Fear of Pain Questionnaire (FPQ): Further psychometric examination in a non-clinical sample. *Pain* 116:339-346, 2005
46. Rowe MK, Craske MG: Effects of varied-stimulus exposure training on fear reduction and return of fear. *Behav Res Ther* 36:719-734, 1998
47. Society for Psychophysiological Research Ad Hoc Committee on Electrodermal M. Publication recommendations for electrodermal measurements. *Psychophysiology* 49:1017-1034, 2012
48. Spielberger CD, Gorsuch R, E Lushene R, Vagg PR, Jacobs G: *Manual for the State-Trait Anxiety Inventory (Form Y1 – Y2)*. Sunnyvale, CA: Consulting Psychologists Press, 1983.
49. Spruyt A, Clarysse J, Vansteenwegen D, Baeyens F, Hermans D: Affect 4.0: A free software package for implementing psychological and psychophysiological experiments. *Exp Psychol* 57:36-45, 2010
50. Sullivan MJ, Bishop SR, Pivik J: The pain catastrophizing scale: Development and validation. *Psychol Assess* 7:524-532, 1995
51. van der Ploeg HMD: Zelf-Beoordelings Vragenlijst: een-Nederlandstalige bewerking van de Spielberger State-Trait Anxiety Inventory STAI-DY. *Tijdschrift Psychiatrie*, 9:576-588, 1982.
52. Vervliet B, Vansteenwegen D, Baeyens F, Hermans D, Eelen P: Return of fear in a human differential conditioning paradigm caused by a stimulus change after extinction. *Behav Res Ther* 43:357-371, 2005
53. Vervoort E, Vervliet B, Bennett M, Baeyens F: Generalization of human fear acquisition and extinction within a novel arbitrary stimulus category. *PLoS One* 9:e96569, 2014
54. Vlaeyen JW: Learning to predict and control harmful events: Chronic pain and conditioning. *Pain* 156(Suppl 1): S86-S93, 2015
55. Vlaeyen JW, Linton SJ: Fear-avoidance and its consequences in chronic musculoskeletal pain: A state of the art. *Pain* 85:317-332, 2000
56. Vlaeyen JW, Linton SJ: Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain* 153:1144-1147, 2012
57. Watson D, Clark LA, Tellegen A: Development and validation of brief measures of positive and negative affect: The PANAS scales. *J Pers Soc Psychol* 54:1063-1070, 1988