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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 one action category (conditioned stimuli; CSs) were followed by pain (CS+; e.g. opening boxes), whereas exemplars of another action category were not (CS-; e.g. closing boxes). Participants reported more pain-related fear and expectancy towards 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 towards 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 take into account in clinical practice.

## 1. Introduction

Fear can be acquired through associative learning. The ability to learn that certain stimuli predict aversive outcomes facilitates the employment of appropriate defensive responses. Since 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.[18, 21, 25, 26] However, when these defensive responses spread to safe stimuli, fear and avoidance may become maladaptive.[35, 36, 38]

Pain is a strong motivator of fear learning as it signals bodily threat. For example, Meulders et al.[41] demonstrated that an initially neutral joystick movement (conditioned stimulus; CS), came to elicit fear and avoidance (conditioned response; CR) after repeated pairings with a painful electrocutaneous stimulus (unconditioned stimulus; pain-US, fear-eliciting CS; CS+), whereas another neutral 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, 28, 56-58] Chronic pain populations indeed have been shown to overgeneralize pain-related fear to non-threatening stimuli.[34, 36, 37] For example, Meulders et al.[36] 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 non-painful CS- movement (GSs-).[36] 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 (i.e. repeated exposure to the GS+ in the absence of the pain-US) was slowed down in chronic pain patients,[37] suggesting they are less successful in updating their pain-related fear or expectancy beliefs even when these are disconfirmed.

Fear learning does not only occur based on perceptual stimulus features: humans also possess the ability to generalize conditioned fear based on semantic relationships between stimuli;[16] a process called *concept-*

*based fear generalization*.[17] 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.[39] showed that pain-related fear can generalize between functionally equivalent actions. Participants acquired fear to unique exemplars of one action category (CS+; e.g. opening boxes), and not the other (CS-; e.g. 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.[39]

Since the original CS+ can be semantically related to many other stimuli that can also trigger feared responses, concept-based fear poses additional challenges to the treatment of maladaptive learned fear.[18, 31] However, the extinction of concept-based pain-related fear has not been investigated before. Therefore, the current study aimed to replicate the acquisition and generalization of conceptual pain-related fear, reported by Meulders et al.,[39] and extend these 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. (3) Finally, based on previous research reporting conceptual fear learning in skin conductance,[16 55] we included this as an additional psychophysiological measure. We expected heightened self-report and psychophysiological measures in response to exemplars of the CS+ category, compared to those of the CS- category during the acquisition and generalization phases, and this difference to disappear during the extinction phase.

## 2. Method and materials

### 2.1 Participants

Fifty-one pain-free volunteers (17 males; mean ± SD age = 31 ± 16 years, range = 17-70) participated in the current study. The sample size was replicated from the original study by Meulders and colleagues.[39] Eighteen participants were psychology students, recruited using the departmental experiment management system of the KU Leuven; they were 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 (e.g. asthma, bronchitis), neurological disease (e.g. 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 (e.g. 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 none of the exclusion criteria applied and signed the informed consent form. The experimental protocol was approved by the Social and Societal Ethics Committee of the KU Leuven (registration number: G-2015 01 147).

### 2.2 Software and stimulus material

The experiment was run on a Windows 8.1 Pro computer (Dell Optiplex 9020) with 8 GB RAM, an Intel Core i7-4790 CPU processor at 3.60 GHz and an AMD Radeon R7 250 graphics card with 2048 MB of video RAM. Stimulus presentations were controlled using the free software package Affect 4.0.[51] Visual stimuli were created using the 3D graphics software Blender 2.72b (Blender Foundation, Amsterdam, The Netherlands).

Conditioned stimuli (CSs) consisted of 20 unique exemplars of two functional action categories: closing and opening boxes (10 open boxes, 10 closed boxes). To avoid overlap between perceptual features, and to thus minimize the possibility of irrelevant perceptual features gaining predictive value, mutually exclusive exemplars were used for both action categories, i.e. a box with a certain combination of color, shape and size could only belong to one of the two action categories. Generalization stimuli (GSs) were 16 novel and unique exemplars of the two 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 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. In order to “open” or “close” the box, participants moved a hydraulic joystick

(Paccus Hawk; Paccus Interfaces BV, Almere, The Netherlands) in the signaled direction (i.e. left or right). During the participants' movement, an animation was played back of the box opening or closing (fig. 1).

The unconditioned stimulus 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) filled with K-Y gel, attached to the wrist of the dominant hand. The intensity of the pain-US was individually determined 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 0-10 pain calibration scale. The mean selected physical stimulus intensity was 27.98 mA (*SD* = 19.52, range = 11–99.9 mA).

2.3 Protocol

We used an adapted version of the voluntary joystick movement (VJM) paradigm[39-41] to investigate the acquisition, generalization and extinction of concept-based pain-related fear. The duration of the experiment was approximately 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 this 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; see Table 1), in order to resolve any problems and questions before the actual experiment started. The presentation order was semi-randomized with the restriction that maximum two consecutive trials could consist of exemplars of the same CS category (i.e. 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 s, after which a box exemplar appeared, accompanied by the *direction signal* (i.e. a red asterisk; see fig. 1). This asterisk appeared for 2 s 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. In this way 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* (i.e. a fixation cross) appeared in the middle of the computer screen to inform the participant that they were to move the joystick in the signaled direction. In the original study by Meulders et al.,[39] the eyeblink startle measure did not corroborate the heightened responding towards exemplars of the CS+ in comparison to those of the CS-, observed in the self-report measures. Meulders et al.[39] suggested that this may be the result of "irrelevant" visual stimulus features gaining predictive value, and being processed earlier than the "relevant", conceptual information, due to the salience and priority of visual information in information processing.[39] 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.[a] During the participant's movement, an animation of the box opening/closing was played back. Once the movement was successfully completed, the box disappeared, and after 8 s a new trial began. When

[a] 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.

participants 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 to prevent possible confounding of the data. This phase consisted of 8 trials of 13 s, with an ITI of 2 s. During each trial, a startle probe of 50 ms was delivered between 8 and 12 s 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 three exceptions. First, there was no longer visual feedback concerning movements (i.e. 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; see 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 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 one of the two functional action categories (e.g. 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 (e.g. 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" section (4 exemplars from each category; randomly distributed across each block).

In the acquisition phase, one startle probe was presented on each trial. A startle probe could appear at one of three 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 s during which a probe could be presented randomly between 4 - 5.5 s after trial onset. The during-CS probe would appear after 500 ms following successful placement of the joystick in its upright position, as described above. The duration of the post-CS ITI period was 8 s, during which the probe could appear randomly at any time between 2.5 - 4.5 s 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 similar 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 one block of 20 trials (see Table 1). Furthermore, these GSs were never followed by the pain-US. In this way, 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, two 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 following the timing described above.

*Extinction phase*. During this 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; see 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.

2.4 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 actually doing so (after presentation of the direction signal and before presentation of the white circle). They were instructed to answer this question by moving the cursor along an 11-point Likert scale ranging from 0 = "Not afraid at all" to 10 = "Very afraid", using the joystick, 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 actually performing the signaled movement. They were instructed to answer these questions by moving the cursor along an 11-point Likert scale ranging from 0 = "Not at all" to 10 = "Very much", using the joystick, and clicking to confirm.

*Eye-blink startle modulation*. The eye-blink startle response is a reflexive cross-species reaction to startle-evoking stimuli (e.g. acoustic startle probes, i.e. sudden loud noises), which can be measured by the tension in the muscles underneath the eye.[4, 13] *Startle modulation*, which refers to potentiation of the startle reflex during states of aversive anticipation, is a widely accepted proxy of conditioned fear.[24, 27] Eye-blink startle responses were measured using three Ag/AgCl Sensormedics electrodes (4 mm) filled with microlyte gel. Two of these electrodes were placed under the left eye to measure electromyographic (EMG) activity, and one 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, USA) with bandpass filter (LabLinc v75-04). The recording bandwith of the signal was between 90 Hz and 500 Hz (approx. 3dB). 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 1000 Hz from 500 ms before the onset of the auditory startle probe until 1000 ms after probe onset (see [40]). Eyeblink startle

responses during the CS/GS movement were taken as an index of cued pain-related fear, while responses during the intertrial interval (ITI) were taken as an index of contextual pain-related fear.

*Skin conductance response*. Skin conductance response relies upon increased eccrine gland (sweat glands found on the palms of the hands and soles of the feet) activity resulting from arousal.[50] Because fear increases arousal levels, elevated skin conductance is widely used a proxy of conditioned fear.[20] Skin conductance was measured using two Biopac EL507 EDA disposable snap electrodes, 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.

2.5 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.

2.6 Post-experimental 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 (FPQ; [32, 48]), the Pain Catastrophizing Scale (PCS; [52]), the Positive and Negative Affect Schedule (PANAS; [19, 59]) and the trait portion of the State-Trait Anxiety Inventory (STAI; [12, 53]). These questionnaires were included for meta-analytical reasons and therefore will not be reported in the current paper.

2.7 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 skin conductance responses) 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.

2.8 Response definition and data analysis overview

*Response definition of the startle response*. Peak startle amplitudes, defined as the maximum of the response curve within 21-175 ms after the startle probe onset, were calculated using the modular script-based program PSPHA.[14] All startle waveforms were visually inspected off-line, 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 in order to optimize visualization and avoid negative values on the *y*-axis.

*Response definition of the skin conductance response*. 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. In order to avoid response artifacts from the pain-US,

statistical analyses were performed on the average skin conductance response (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, Mass). Response amplitudes (uSiemens) were calculated per trial whereby the maximum value is subtracted from a preceding lower value (i.e. baseline) in the time window of the movement. To account for inter-individual differences between participants, *z*-transformations were carried out on each raw skin conductance response and then converted to *T*-scores. All trials where the 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 samples *t*-tests were run on practice phase data and separate repeated measures (RM) 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 $\eta_p^2$ 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).

## 3. Results

### 3.1 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), a 8 (Feature: CS+, CS-, left, right, dark, light, small, large) x 8 (Block: ACQ1-3, GEN, 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, $F(1, 50) = 1.54$, $p = .220$, $d = 0.35$. 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 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, $F(1, 50) = 0.9$, $p = .35$ (fig. 2).

*Retrospective pain intensity and unpleasantness ratings*. A 2 (Rating: Intensity, Unpleasantness) x 4 (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).

### 3.2 Prospective fear of movement-related pain ratings

*Practice*. Paired samples *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, $t(50) = 1.587$, $p = .199$, confirming the absence of baseline differences in fear responding between the CS categories.

*Acquisition*. A 2 (Stimulus Category: CS+, CS-) x 3 (Block: ACQ1-3) RM ANOVA was carried out on the mean pain-related fear ratings for the CS categories during the three 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 x Block interaction, $F(2, 100) = 12.82$, $p = < .001$, $\varepsilon = .98$, $\eta_p^2 = .20$, suggesting that fear towards

the respective CS category was acquired over time. Planned comparisons confirmed that although there was no significant difference in the first acquisition block, $F(1, 50) = 3.19$, $p = .080$, $d = 0.5$, in the second acquisition block, exemplars of the CS+ category elicited more pain-related fear than did those of the CS- category, $F(1, 50) = 20.78$, $p < .001$, $d = 1.29$. 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, a RM ANOVA with Stimulus Category (GS+, GS-, CS+, CS-) as a within-subjects variable was conducted on prospective fear ratings during the generalization phase. This analysis yielded a significant main effect of Stimulus Category, $F(3, 150) = 19.07$, $p < .001$, $\varepsilon = 0.53$, $\eta_p^2 = .28$. 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 to 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 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 (Stimulus Category: CS+, CS-) x 5 (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 x 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).

### 3.3 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 both ratings and for sake of brevity, we did not include a detailed report of the results here. The complete results of the RM ANOVA, and planned contrasts for these ratings, as well as the results of the Spearman's  correlational analyses between pain-related fear and US-expectancy, were added as supplementary online material.

### 3.4 Eyeblink startle modulation

*Acquisition*. A 3 (Stimulus Type: CS+, CS-, ITI) x 3 (Block: ACQ1-3) RM ANOVA was conducted on the mean startle amplitudes during probes presented during exemplars of the CS+ and CS- categories as well as 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 x 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, $F(1, 50) = .33$, $p = .568$, $d = 0.16$, nor the last, $F(1, 50) = .04$, $p = .837$, $d = 0.06$, acquisition block. Yet, 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. Due to the lack of differential acquisition effect in the eyeblink startle responses, we do not further report the generalization and differential extinction effects (fig. 5).

### 3.5 Skin conductance response

*Acquisition*. A 2 (Stimulus Type: CS+, CS-) x 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 the lack of differential acquisition effect in the SCRs, we did not further test and report generalization and differential extinction effects.

## 4. Discussion

Humans can acquire fear based on conceptual knowledge. The aim of the current study was to replicate the previously demonstrated[39] acquisition and generalization of concept-based pain-related fear, and to investigate whether such fear could subsequently be extinguished. An additional aim was to investigate whether methodological modifications, i.e. (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.[39]

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 to the CS- category. However, in line with the original study by Meulders et al.,[39] exemplars of both CS categories elicited higher startle responses than the context alone (i.e., ITI startle responses), again suggesting elevated, but non-differential, fear towards both CS categories, compared to 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, following 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 to the CS- category were not observed in our psychophysiological

measures. These results correspond to those previously reported by Meulders et al..[39] The authors[39] suggested the non-differential startle responses between CS categories to have 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, due to its salience, visual information is often processed faster than other information.[22, 46] 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, since joystick movements in one direction were partially reinforced (i.e. half of the movements to the right/left were followed by pain), movement directions may have produced a level of fearful responding in their own right. 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). Yet given that two previous studies employing 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.[33, 39]

The current results are in contrast with previous research reporting observable concept-based learning in SCRs. Dunsmoor et al.[16] showed elevated SCRs and pain expectancy ratings in response to exemplars of a superordinate category paired with a painful shock (e.g. pictures of animals), compared to exemplars of another superordinate category, not paired with shock (e.g. pictures of tools). Vervoort et al.[55] reported heightened SCRs in response to a CS+, and these generalized to other members of the learnt CS+ category. Our study differs from those of Dunsmoor et al.[16] and Vervoort et al.[55] 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). Due to 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). Since the SCR is a long latency response that takes time to start and peak (the response typically starts 1-4 s post stimulus presentation, and peaks 0.5-5 s later),[5, 30] 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.[39], who demonstrated that pain-related fear can be acquired and generalized based on conceptual knowledge about category membership. Furthermore, they 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,[15, 23, 47] and chronic pain conditions specifically.[2, 44 29] 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 original[39] and current studies, compared to previous studies investigating fear of movement-related pain using the VJM paradigm.[42] 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 (e.g. 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 also take longer to generalize that rule. In line with this, Vervoort et al.[55] found that extinction of concept-based learning to the original CS+ spreads to conceptually related GSs, but not the other way round,[55] 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, 49, 54] Since 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.[45] For instance, the use of more than one fear-eliciting stimuli 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,[34, 37] 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] like 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 to expectancy measures,[43] 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 where 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, yet this was not possible using the current set-up.

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 (e.g. perceptual or conceptual). Since fear may originally be acquired based on conceptual information, it may prove more useful to identify and target fear beliefs towards the conceptual category, rather than the perceptual stimulus features, which are also present, but 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.

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**Figure captions**

*Figure 1*. Schematic overview of the experimental task.

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

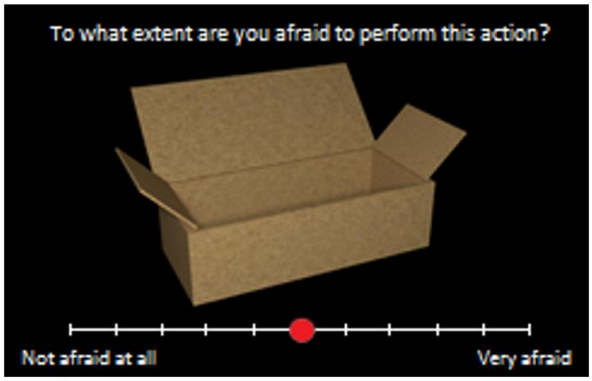
*Figure 3*. Mean ratings of retrospective pain-US intensity and unpleasantness during the acquisition (ACQ1-3) and generalization (GEN) phases. Error bars represent 95% confidence intervals.

*Figure 4*. Mean prospective self-reported fear of movement-related pain 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.

*Figure 5*. 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.

*Figure 6*. 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.

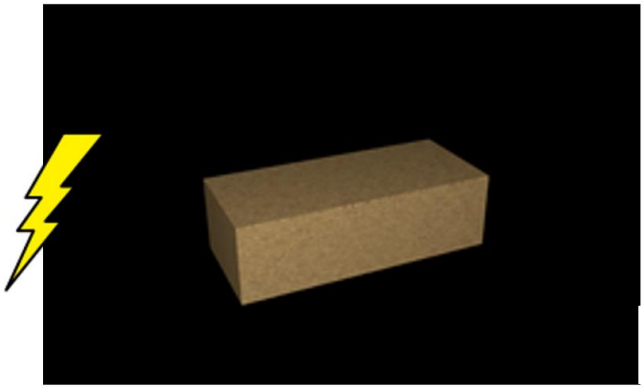
6000 ms: An open or closed box exemplar is presented and a red asterisk (direction signal) appears for 2000 ms indicating the direction of the upcoming joystick movement.




The direction signal disappears, and occasionally questions concerning prospective pain-related fear and pain-US expectancy are presented together with a Likert scale.

Upon the disappearance of the direction signal (or after responding to self-report questions where applicable), a white circle appears indicating the onset of the upright joystick movement.

Once the joystick has been successfully moved into the upright position, the circle disappears and a fixation cross (starting signal) appears, informing the participant that it is time to initiate the movement.



During the joystick movement, an animation of the box opening/closing is shown. In the case of a CS+ trial, the pain-US is delivered after the movement in 80% of the trials, and after 8000 ms a new trial begins.

*t/ms*

Figure2
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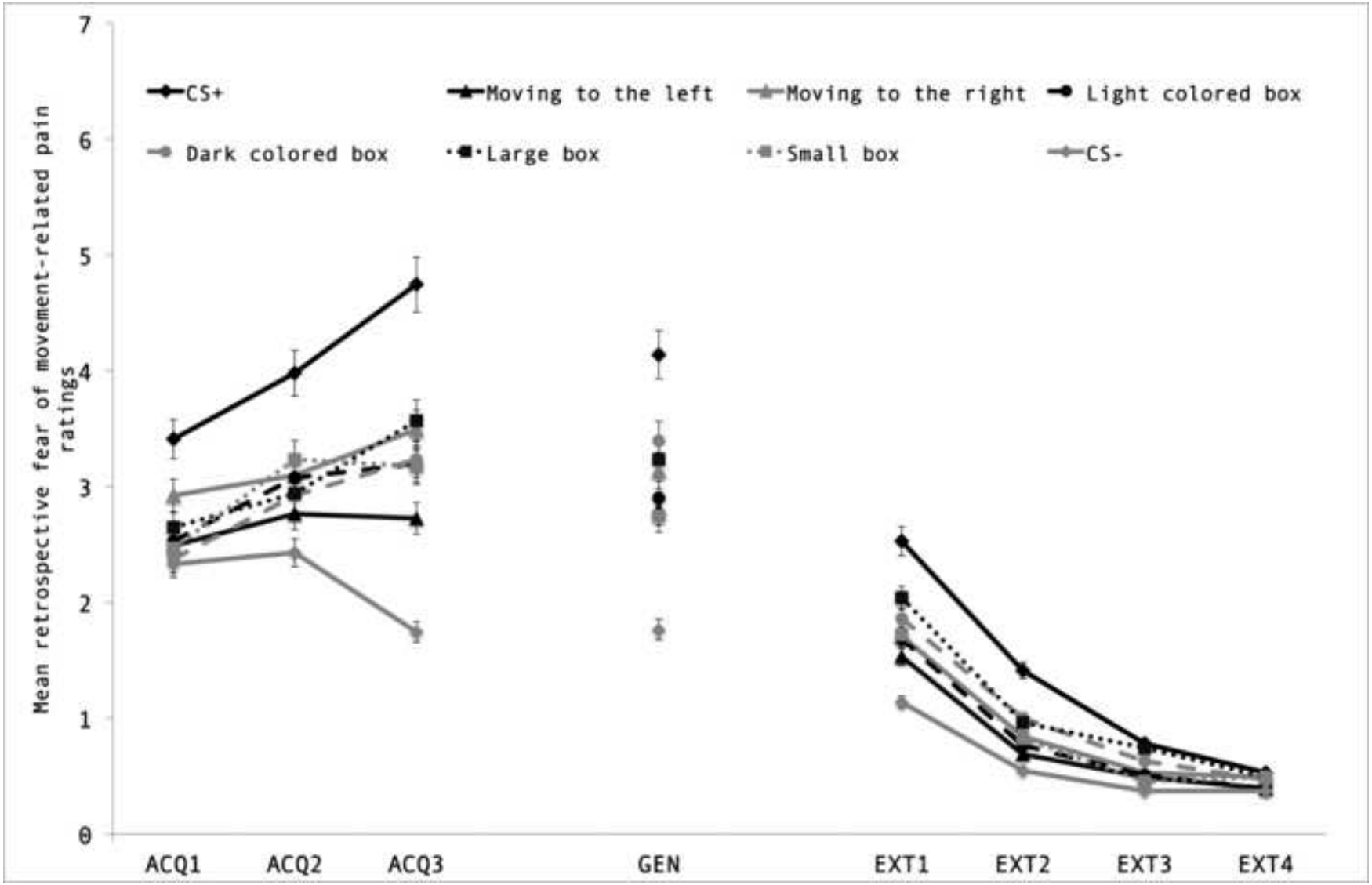

Figure3
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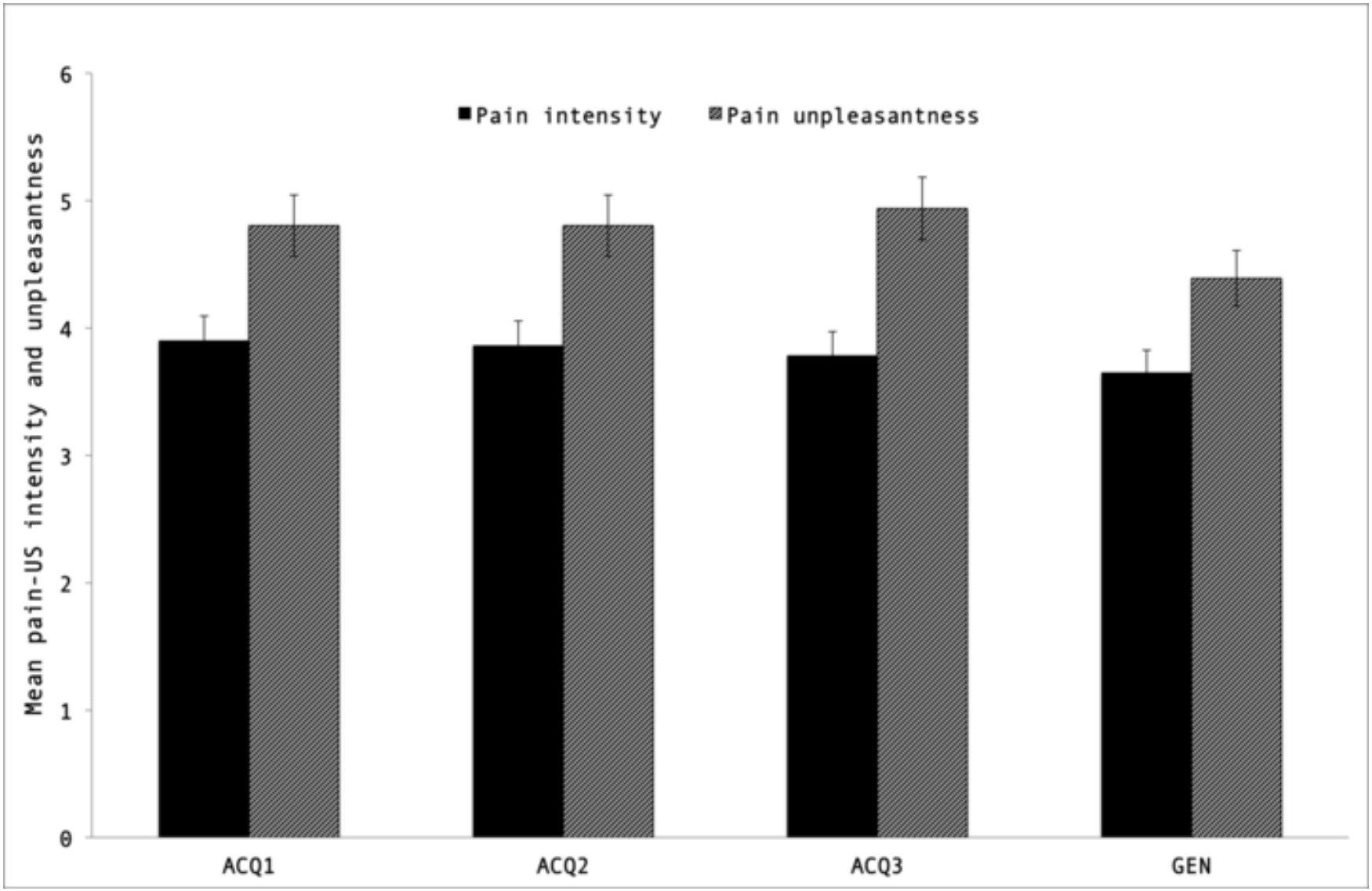

Figure4
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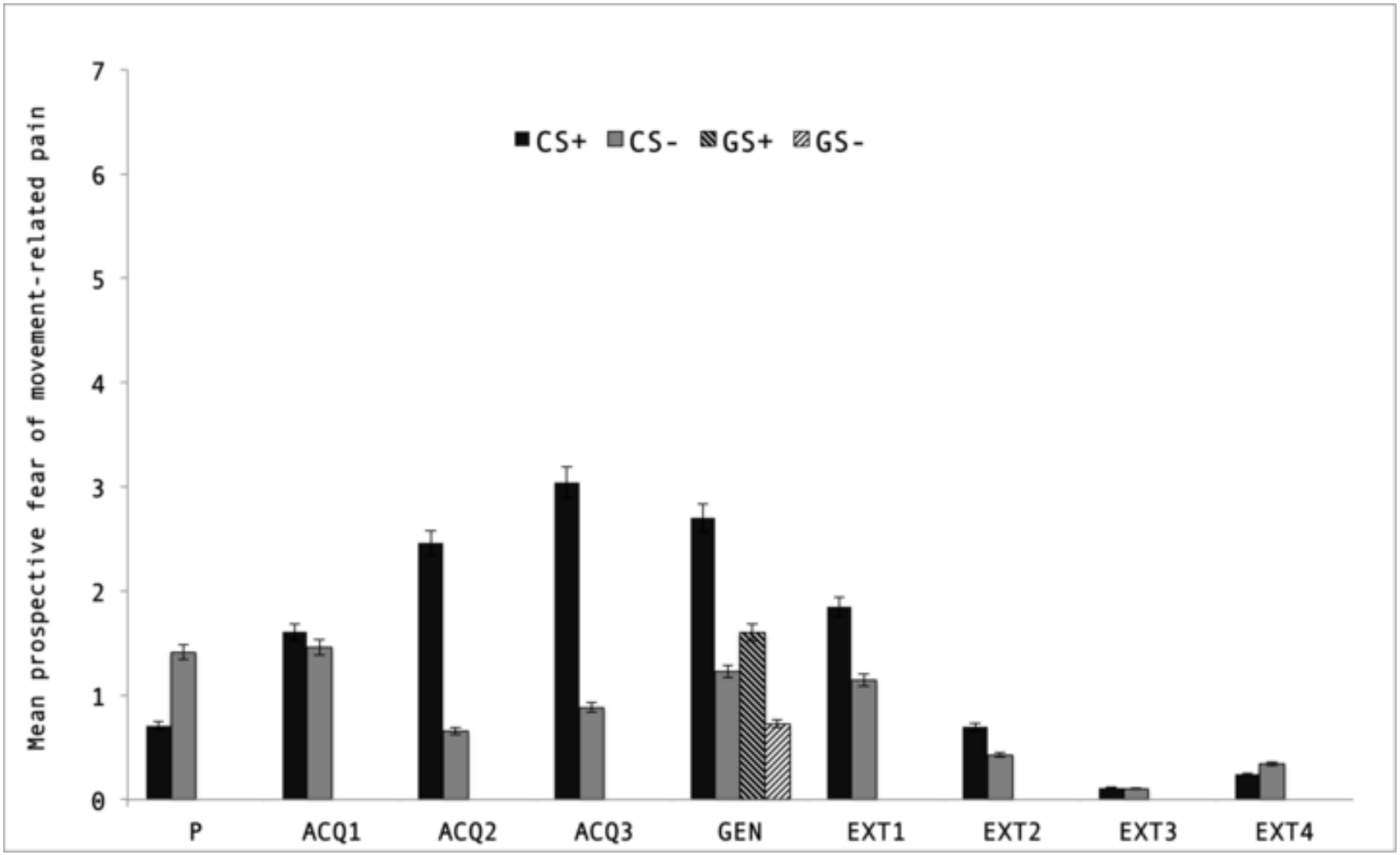

Figure5
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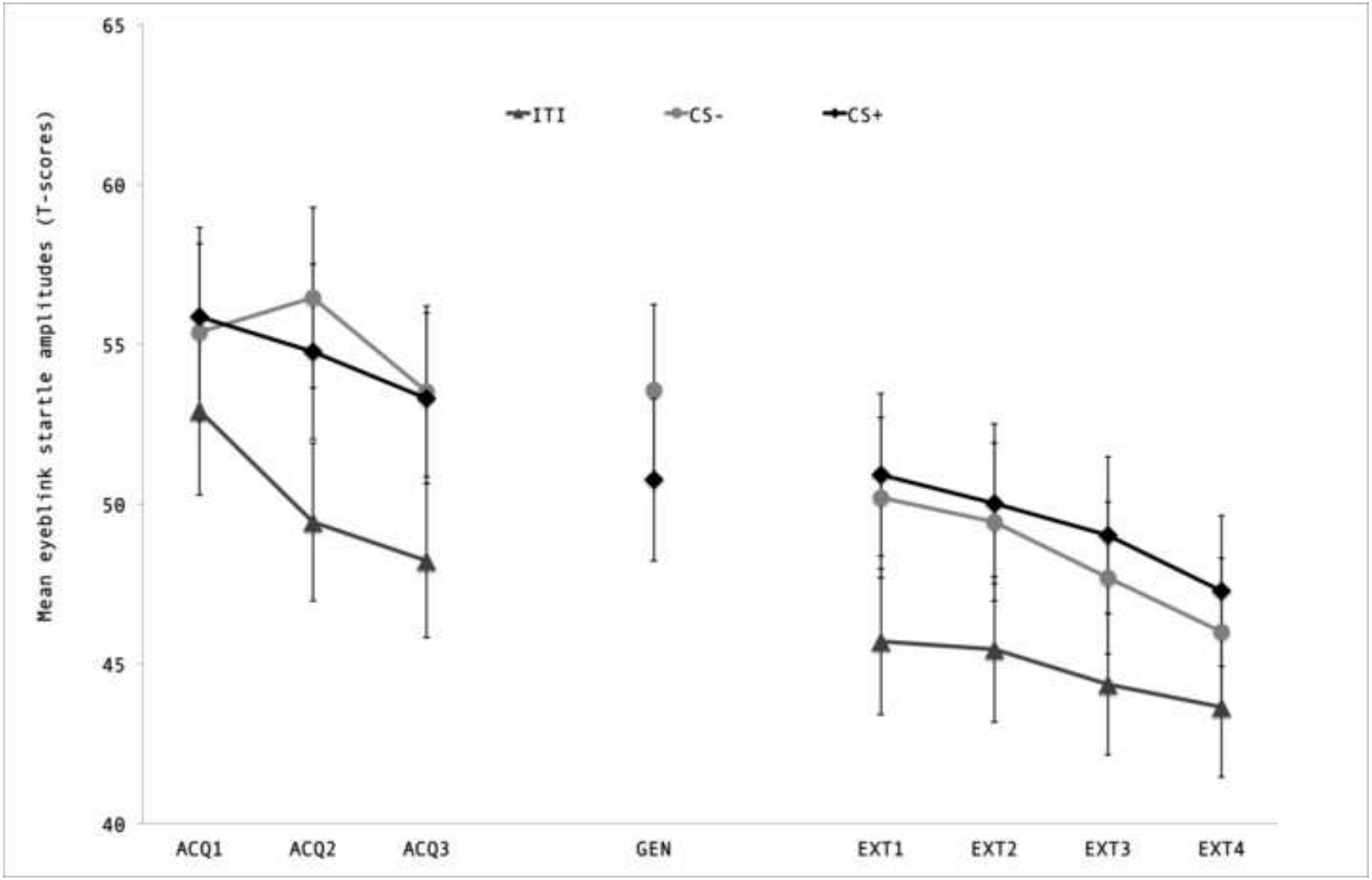

Figure6
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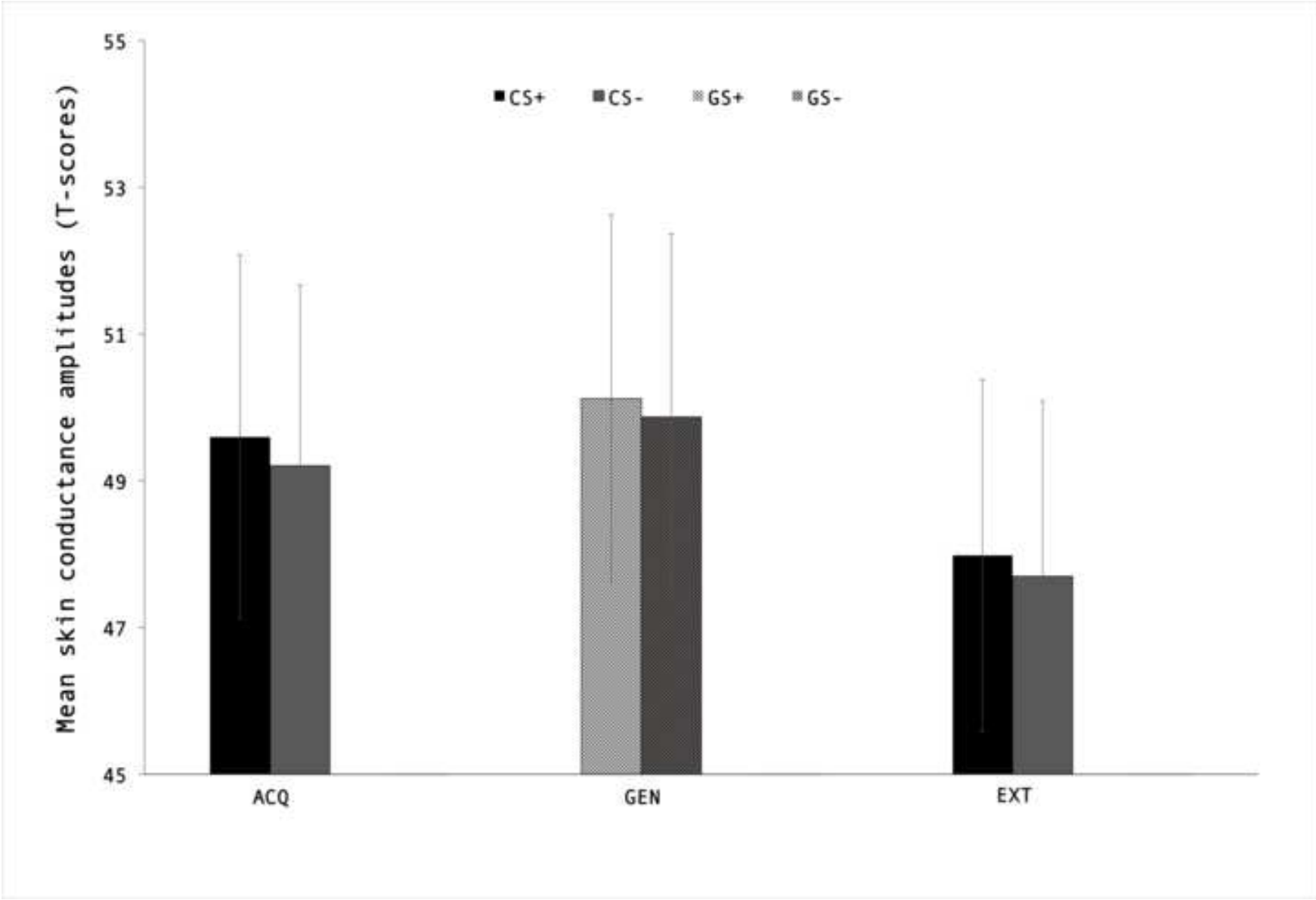

**Figure S1 supplementary material**

*Figure S1*. Mean prospective self-reported pain-US expectancy 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.

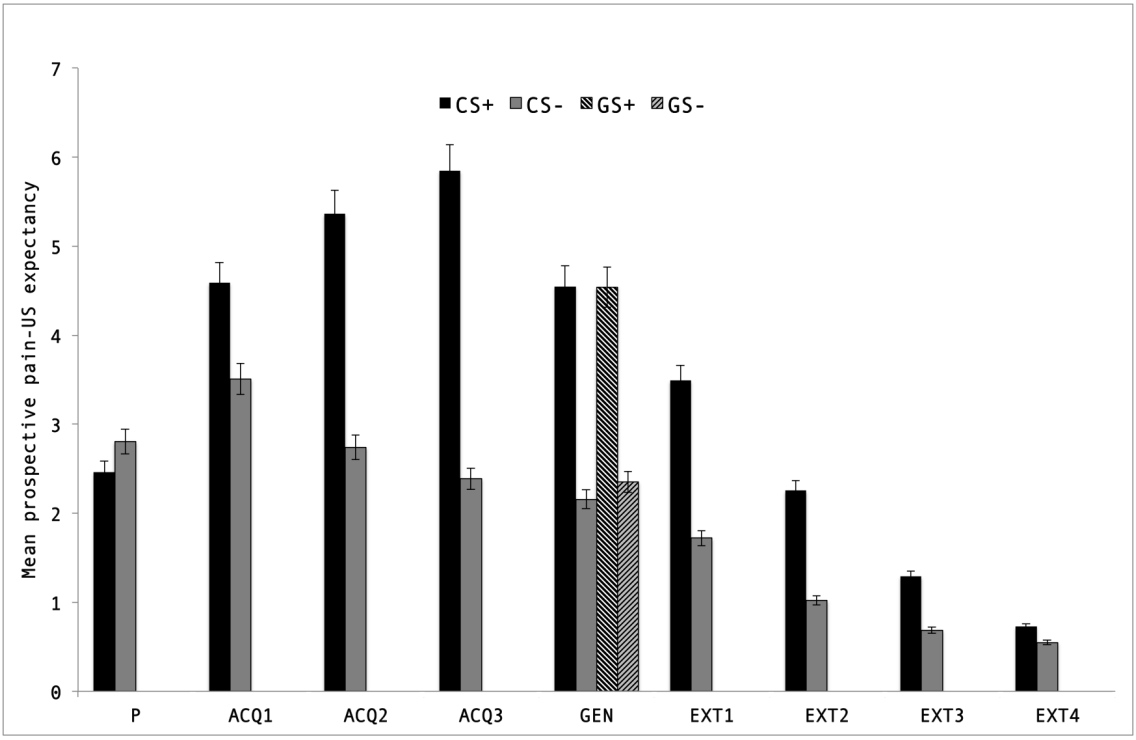

*Table 1. Study design summary*

| Practice phase (12 trials) | Startle habituation phase (8 trials) | Acquisition phase (3 x 20 trials) | Generalization phase (20 trials) | Extinction phase (4 x 20 trials) |
|---|---|---|---|---|
| | | | 8 GS+ | |
| 6 CS+ | | 3 x 10 CS+ | 8 GS- | 4 x 10 CS+ |
| | 8 trials | | | |
| 6 CS- | | 3 x 10 CS- | 2 CS+ | 4 x 10 CS- |
| | | | 2 CS- | |

*Note* – CS = conditioned stimulus; 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 = generalization stimulus; 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.

**Table S1 supplementary material**

*Table S1. Spearman's ρ correlation coefficients between fear of movement-related pain and US-expectancy ratings during each block for each CS/GS type separately.*

| Block | ρ (CS+ fear, CS+ expectancy) | ρ (CS- fear, CS- expectancy) | ρ (GS+ fear, GS+ expectancy) | ρ (GS- fear, GS- expectancy) |
|---|---|---|---|---|
| **ACQ1** | $\rho$ = .270 | $\rho$ = .565** | | |
| **ACQ2** | $\rho$ = .333* | $\rho$ = .611** | | |
| **ACQ3** | $\rho$ = .508** | $\rho$ = .736** | | |
| **GEN** | $\rho$ = .638** | $\rho$ = .737** | $\rho$ = .668** | $\rho$ = .733** |
| **EXT1** | $\rho$ = .579** | $\rho$ = .495** | | |
| **EXT2** | $\rho$ = .779** | $\rho$ = .863** | | |
| **EXT3** | $\rho$ = .699** | $\rho$ = .722** | | |
| **EXT4** | $\rho$ = .820** | $\rho$ = .832** | | |

*Note* - Degrees of freedom are 50 for all correlations. * = significant correlation at the .05 level, ** = significant correlation at the .01 level.

## Supplementary material: Statistical analyses of the prospective pain-US expectancy ratings

*Practice*. Paired samples *t*-tests were conducted on the mean prospective pain-US expectancy ratings for the CS+ and CS- categories during the practice phase. This analysis confirmed no significant differences in prospective US-expectancy ratings, $t(50) = 1.806$, $p = .077$, between the CS+ and CS- categories before conditioning.

*Acquisition*. A 2 (Stimulus Category: CS+, CS-) x 3 (Block: ACQ1-3) RM ANOVA was carried out on the mean pain-US expectancy ratings for the CS categories during the three acquisition blocks. This analysis showed a significant main effect of Stimulus Category, $F(1, 50) = 52.58$, $p < .001$, $\eta_p^2 = .51$, and Block, $F(2, 100) = .07$, $p = .901$, $\varepsilon = .82$, $\eta_p^2 = .001$, both of which were qualified by a significant Stimulus Category x Block interaction, $F(2, 100) = 19.68$, $p < .001$, $\varepsilon = .98$, $\eta_p^2 = .28$. Planned comparisons confirmed that exemplars of the CS+ category induced higher pain-US expectancy compared to the exemplars of the CS- category during the first acquisition block (ACQ1), $F(1, 50) = 13.95$, $p < .001$, $d = 1.06$. This difference remained significant during the last acquisition block (ACQ3), $F(1, 50) = 62.68$, $p < .001$, $d = 2.24$ (fig. 3).

*Generalization*. To investigate generalization of pain-US expectancy to the novel exemplars (GSs) of the learned CS categories, a RM ANOVA with Stimulus Category (GS+, GS-, CS+, CS-) as a within-subjects variable was conducted on prospective pain-US expectancy ratings during the generalization phase. There was a significant main effect of Stimulus Category, $F(3, 150) = 25.78$, $p < .001$, $\varepsilon = .52$, $\eta_p^2 = .34$. Planned comparisons confirmed that participants expected the pain-US to occur more during the original exemplars of the CS+ category compared to during the exemplars of the CS- category, $F(1, 50) = 23.21$, $p < .001$, $d = 1.36$. Furthermore, in line with our hypothesis, participants reported higher pain-US expectancy in response to novel exemplars of the CS+ category (GS+), compared to those of the CS- category (GS-), $F(1, 50) = 40.48$, $p < .001$, $d = 1.80$. As expected, no such differences occurred between the CS+ and GS+ exemplars, $F(1, 50) = .0007$, $p = .980$, $d = .01$ or the CS-

and GS- exemplars, $F(1, 50) = 1.21$, $p = .276$, $d = .31$, again suggesting successful and complete transfer of learned contingencies to novel exemplars of the CS categories (fig. 3).

*Extinction*. A 2 (Stimulus Category: CS+, CS-) x 5 (Block: ACQ3, EXT1-4) RM ANOVA was carried out on the mean prospective pain-US expectancy ratings during the extinction phase. There was a significant main effect of Stimulus Category, $F(1, 50) = 64.47$, $p < .001$, $\eta_p^2 = .56$, and Block, $F(4, 200) = 83.59$, $p < .001$, $\varepsilon = .62$, $\eta_p^2 = .63$, both of which were qualified by a significant Stimulus Category x Block interaction, $F(4, 200) = 25.14$, $p < .001$, $\varepsilon = .66$, $\eta_p^2 = .34$. Planned comparisons confirmed that the significant difference between pain-US expectancy ratings for the CS+ and CS- category, evident in the last acquisition block, remained as such during the first extinction block, $F(1, 50) = 27.55$, $p < .001$, $d = 1.48$. In the last extinction block, this difference was no longer significant, $F(1, 50) = 2.86$, $p = .097$, suggesting successful extinction of category-based pain-US expectancy (fig. 3).