Published in final edited form as:

Acta Psychol (Amst). 2018 March ; 184: 75–84. doi:10.1016/j.actpsy.2017.09.009.

Generalization of learned pain modulation depends on explicit learning

Leonie Koban^{1,2,*}, Daniel Kusko^{1,*}, and Tor D. Wager^{1,2}

¹Department of Psychology and Neuroscience, University of Colorado Boulder

²Institute of Cognitive Science, University of Colorado Boulder

Abstract

The experience of pain is strongly influenced by contextual and socio-affective factors, including learning from previous experiences. Pain is typically perceived as more intense when preceded by a conditioned cue (CS_{HIGH}) that has previously been associated with higher pain intensities, compared to cues associated with lower intensities (CS_{LOW}). In three studies (total N=134), we tested whether this *learned pain modulation* generalizes to perceptually similar cues (Studies 1 and 2) and conceptually similar cues (Study 3). The results showed that participants report higher pain when heat stimulation was preceded by novel stimuli that were either perceptually (Studies 1 and 2) or conceptually (Study 3) similar to the previously conditioned CS_{HIGH}. Across all three studies, the strength of this generalization effect was strongly correlated with individual differences in explicitly learned expectations. Together, these findings suggest an important role of conscious expectations and higher-order conceptual inference during generalization of learned pain modulation. We discuss implications for the understanding of placebo and nocebo effects as well as for chronic pain and anxiety.

Keywords

Pain; Conditioning; Learning; Placebo effect; Instruction; Generalization; Conceptual

Introduction

How we experience a painful event is strongly influenced by our prior learning history. In line with this idea, previous research has shown that classical conditioning not only alters the fear response to learned stimuli previously paired with painful shocks, but also changes the experience of the *pain itself* (Atlas, Bolger, Lindquist, & Wager, 2010; Atlas et al., 2012; Koban & Wager, 2016; Voudouris, Peck, & Coleman, 1990). In such *learned pain modulation* paradigms, one stimulus (the CS_{HIGH}) is first consistently followed by high pain

Please address correspondence to: Dr. Leonie Koban, Department of Psychology and Neuroscience, and Institute of Cognitive Neuroscience, leonie.koban@colorado.edu, telephone: (720) 525-8804.

* Authors contributed equally to this research

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and another stimulus (CS_{LOW}) by low pain. In a subsequent test phase, identical noxious stimulation is perceived as more painful, when preceded by the CS_{HIGH} compared to the CS_{LOW} (Atlas et al., 2010; for reviews, see Atlas & Wager, 2012; Colloca & Miller, 2011; Colloca, Sigaud, & Benedetti, 2008; Voudouris et al., 1990). Classical conditioning has further been shown to be a powerful factor in generating placebo and nocebo responses, i.e. beneficial or harmful effects based on patients' expectations when receiving an inert treatment (Amanzio & Benedetti, 1999; Colloca & Grillon, 2014; Kirsch, 2004; Montgomery & Kirsch, 1997). Despite the growing evidence supporting the importance of learning in pain modulation, much less is known about whether learned pain modulation may also *generalize* to novel but perceptually or conceptually similar stimuli.

Generalization can be defined as transfer of previously learned information to novel stimuli and situations, often as a function of similarity between the original and a novel situation. For example, having a painful experience with a tooth removal may result in fear and avoidance of other dental procedures, too. Generalization of learned appetitive and aversive responses has been demonstrated across numerous species. For instance, pigeons can be trained to peck a key in order to receive food based on color, and this behavior generalizes to perceptually similar key colors along a similarity gradient (Guttman & Kalish, 1956). Human studies have demonstrated generalization gradients in physiological and behavioral threat responses in conditioned shock paradigms (reviewed by Dunsmoor & Paz, 2015; Lissek et al., 2008; Meulders & Vlaeyen, 2013; Onat & Büchel, 2015) and following reward learning (Kahnt, Park, Burke, & Tobler, 2012). Generalization of conditioned threat can also be based on *conceptual* relationships among cues (Bennett, Hermans, Dymond, Vervoort, & Baeyens, 2015; Bennett, Vervoort, Boddez, Hermans, & Baeyens, 2015; Boddez, Bennett, Esch, & Beckers, 2016; Dunsmoor & LaBar, 2012; Dunsmoor & Murphy, 2014; Maltzman, 1977; Meulders, Vandael, & Vlaeyen, 2017). For example, fear of tooth removal may generalize to conceptually related stimuli, such as dentist chairs or tools, and even to reading or hearing the word “dentist”. Thus, instead of just being similar in terms of physical features, different concepts can also be similar in terms of their *meaning*, even if there is a lack of perceptual similarity. The aim of the present study was to investigate whether perceptual and conceptual generalization can also modify the response to pain (as the UCS) itself.

Another important question we addressed concerns the role of conscious expectations and conceptual processing in classical conditioning (Kirsch, 2004; Rescorla, 1988) and in learned pain modulation (Jensen et al., 2012; Jepma & Wager, 2015; Koban & Wager, 2016). Several studies have shown that learned pain modulation is mediated by changes in explicit expectations (Jepma & Wager, 2015; Koban & Wager, 2016; Rosén et al., 2016) and dependent on contingency awareness (Harvie et al., 2016). Others have shown that subliminal stimuli can be sufficient to activate pain-modulatory cue representations and possibly even induce learned pain modulation (Jensen et al., 2014; Jensen et al., 2012). Although there is a growing consensus that conditioning and pain modulation typically involve conscious awareness as well as unconscious systems (Amanzio & Benedetti, 1999; Benedetti et al., 2003; Hofmann, De Houwer, Perugini, Baeyens, & Crombez, 2010; Lovibond & Shanks, 2002), generalization has been theorized to be an active cognitive process seen only after explicit learning occurs (Dunsmoor & Murphy, 2015; Guttman &

Kalish, 1956; Pearce, 1987). If so, generalization might require conscious expectation during learning as well. Currently, it is unknown whether explicit learning and expectations are important for generalization of learned pain modulation.

In three experiments, we therefore tested the following research questions. First, does learned pain modulation generalize to perceptually similar cues, such as Gabor patches (i.e., sinusoidal gratings of lines at different orientations) with similar spatial orientations (Studies 1 & 2)? Second, does generalization also extend to *conceptually* similar cues, such as from one animal drawing to other visual presentations (e.g. photos, words) of this animal, and even to other animals (Study 3)? And third, does generalization of learned pain modulation depend on explicit awareness of the cue-pain relationship during conditioning (Studies 1–3)? Each experiment consisted of a learning phase, in which healthy volunteers learned the relationship between two cues (CS_{HIGH} and CS_{LOW}) and varying levels of subsequent painful thermal stimulation. This learning phase was followed by a generalization phase, in which perceptually (Studies 1 and 2) or conceptually (Study 3) similar stimuli to the CS_{HIGH} and CS_{LOW} preceded the thermal stimulation. In all three experiments, we measured expectations, pain ratings, and skin conductance responses to the painful heat stimuli as dependent measures. We predicted that a) people would generalize learned pain modulation to novel stimuli as a function of perceptual or conceptual similarity to the CS, and b) that generalization would depend on explicit expectations during the learning phase.

Overview: Study 1

The first experiment tested the generalization of learned visual cue effects on pain along a perceptual similarity gradient. In a first, learning phase, participants were conditioned to associate one of two Gabor patches (the CS_{LOW}) with lower, and the other Gabor patch cue with higher pain (CS_{HIGH}). During generalization they received pain preceded by novel Gabor patches with orientations between and beyond the original learning cues (see Figure 1 for an overview).

Methods: Study 1

Participants—Thirty-eight healthy volunteers completed the experiment (16 female, mean age = 26.6). All participants were free of psychiatric, neurological, and pain conditions. One additional participant did not complete the task due to high pain sensitivity, and another additional participant was excluded due to a clinical diagnosis. All participants gave written informed consent form and were paid at the conclusion of the experiment. The University of Colorado Institutional Review Board approved the study.

Stimuli—During learning, pain was preceded by one of two Gabor patches with different orientation angles (35° and 55°, see Figure 1A). One of those cues was always followed by low to medium temperature stimulation (CS_{LOW}, 47 or 48°C, 50% each), the other cue by medium or high thermal stimulation heat (CS_{HIGH}, 48 or 49°C, 50% each). Assignment of the orientation angle to CS condition was counterbalanced across participants. Note that the medium temperature trials in both CS conditions allowed us to test the effects of learning on pain independent of nociceptive stimulus input. These temperatures (47–49°C) have been shown to be painful but tolerable for most people and to activate pain-specific brain

responses in an increasing linear fashion (Clark, 2003; Coghill, Sang, Maisog, & Iadarola, 1999; Krishnan et al., 2016; Wager et al., 2013). A calibration procedure that preceded the experimental tasks further ensured that all participants rated the temperatures as painful but tolerable.

A second set of Gabor patches with angles of 25°, 29°, 33°, 37°, 41°, 45°, 49°, 53°, 57°, 61°, and 65° served as stimuli for the generalization task. The generalization cues had orientations between and beyond CS_{LOW} and CS_{HIGH}, but did not include the original CS from the learning phase. The original CS_{LOW} and CS_{HIGH} were not repeated in the generalization phase in order to test for generalization to purely novel stimuli, as function of the distance to the CS_{high} and CS_{low}, in line with a previous study that has tested generalization of learned associations using similar stimuli (Kahnt, et al., 2012). Heat pain stimuli during the generalization task were always at a medium level of heat intensity (48°C), and thus the same for all generalization cues.

Thermal stimuli were applied to five different skin sites on the left volar forearm using a CHEPS thermode (27mm diameter) and controlled by a Pathway system and software (Medoc Advanced Medical Systems, Israel). One out of five different skin sites was selected at random before each run and used for the thermal pain stimulation in all trials of that run (for both learning and generalization task). Baseline temperature was set to 32°C. Heat pain stimulation was delivered in short epochs with 40°C/s ramp rate and 1s plateau duration at target temperatures.

Procedures—Participants first underwent five blocks of the learning task (16 trials each), before performing five blocks of the generalization task, which included 11 trials each (see Fig. 1B). All of the 80 trials in the learning phase started with the presentation (4s) of one of the learning cues (CS_{LOW} or CS_{HIGH}). Cues were immediately followed by an expectation rating (“How much pain do you expect?”, no time limit to respond), which allowed us to assess explicit pain expectations and learning about the cues over time. Immediately after their rating, participants received a short (1s plateau) heat pain stimulation to the left volar forearm. After a jittered waiting period (3–5s), they rated how much pain they actually felt. Inter-trial fixation cross duration was jittered between 6.5–9s.

All of the 55 generalization trials started with the presentation (4s) of one of eleven generalization cues, followed by medium temperature heat pain stimulation (48°C, 1s plateau duration). Following a brief jittered waiting screen (3.5–6.5s), participants rated the experienced pain on a visual analog scale. Inter-trial duration was jittered between 5.5–8s.

Skin Conductance—Electrodermal activity was measured at the index and middle fingers of the left hand and recorded using a BIOPAC MP150 system and Acknowledge software at 500Hz sampling rate. Single trial-wise skin conductance response (SCR) was analyzed using the SCRalyze toolbox (Bach, Flandin, Friston, & Dolan, 2009). SCRalyze uses a general linear model approach to reliably estimate SCR to rapidly presented stimulus events (Bach, Flandin, Friston, & Dolan, 2010). The filtered (1Hz low pass) skin conductance time series data was normalized for each subject. Then, regressors for pain onsets in each trial in the generalization task were convolved with a canonical skin conductance response function

(Bach et al., 2010) and fitted to the skin conductance time series, yielding estimates (in the form of beta weights) for the amplitude of pain-evoked skin conductance responses for each trial. For visual display, filtered SCR time courses were segmented into epochs starting two seconds before until eight seconds after the thermal stimulation was initiated and baseline corrected by subtracting the average value within the two seconds preceding the thermal stimulus onset.

Statistical Analysis—Expectancy and pain ratings were acquired on visual analog scales (VAS) ranging from ‘absolutely no pain’ to ‘worst pain imaginable’ (in the context of the experiment), ranging from 0 to 100 (where 100 indicating highest pain or pain expectancy ratings). We used a multi-level robust general linear model (GLM) to test how CS (in the learning phase) and Gabor angle (during the generalization phase, coded as a linear predictor from -5 to 5) affected expectation ratings, pain ratings, and single trial beta estimates for SCR to pain. The code for the multi-level GLM is available at <https://github.com/canlab>. A significance level of $p < 0.05$ was applied to all analyses unless indicated otherwise.

Results: Study 1

Learning Task—During learning, expectation ratings (illustrated in Fig. 2A) were significantly higher in CS_{HIGH} ($M=54.0$, $STD=23.1$) than CS_{LOW} trials ($M=47.6$, $STD=22.9$), $t(37) = 4.54$, $p < 0.001$, Cohen’s $d = 0.74$. Pain ratings showed a strong effect of stimulation temperature, (see Fig. 2B), $t(37) = 12.51$, $p < 0.001$, Cohen’s $d = 2.03$. Further, pain ratings for the medium heat stimulation (48°C) were significantly higher when preceded by the CS_{HIGH} ($M=53.2$, $STD=24.4$) than when preceded by the CS_{LOW} ($M=49.8$, $STD=24.7$), $t(37) = 3.83$, $p < 0.001$, Cohen’s $d = 0.62$ (see Fig. 2B), thus replicating previous findings of learned pain modulation (Atlas et al., 2010; Colloca, Tinazzi, et al., 2008; Koban & Wager, 2016). A similar trend, albeit less strong, was observed for SCR to pain (CS_{LOW} $M=1.08$, $STD=0.79$ vs. CS_{HIGH} $M=1.21$, $STD=0.87$), $t(37) = 1.82$, $p = 0.077$, Cohen’s $d = 0.30$. This suggests that people learned to associate the two different cues with higher and lower pain expectations, which in turn influenced their experiences of the pain itself (see Koban and Wager, 2016).

Generalization Task—In contrast to our hypothesis, we did not observe a significant main effect of Gabor angle on pain ratings during the generalization, $t(37) = 1.16$, $p = 0.25$ (see Figure 2C and Suppl. Table S2). However, there was substantial variability in how much people learned about the CS during the initial learning phase. Thus, we tested whether generalization depended on how much participants learned about the CS in the learning phase, by using the individual beta estimates from the cue (CS_{HIGH} versus CS_{LOW}) effects on expectations (in the learning task) as a 2nd level moderator. In line with the hypothesis that generalization depends on explicit learning, we found a significant positive modulation of generalization by individual differences in learning, $t(36) = 2.50$, $p = 0.017$, Cohen’s $d = .41$ (see Figure 2D, scatter plot). We then performed a median split based on learned cue effects on expectations, resulting in two subgroups of participants, labeled as *Learners* and *Non-learners*. Whereas the Learners showed a significant effect of Gabor angle on medium pain ratings during the generalization task, $t(18) = 2.74$, $p = 0.014$, Cohen’s $d = 0.63$, this effect was not present for the Non-learners, $t(18) = -0.97$, $p = 0.344$ (see Suppl. Figure S1).

In contrast to the pain ratings, SCR (see Fig. 2E) were not significantly modulated by Gabor angle, nor was such a relationship modulated significantly by individual differences in cue-learning (all p 's > 0.20), potentially due to lack of power, habituation of SCR across time, or extinction. In sum, these findings suggest that the degree to which people explicitly learned about the cue-pain relationship in the learning task, was critical for determining whether they would generalize this learnt pain modulation to perceptually similar but novel cues.

Overview: Study 2

The second study aimed at replicating the generalization of learned pain modulation in an independent and larger sample. The learning phase of this second study, which also included an independent social influence manipulation, has been reported previously (Koban & Wager, 2016). As in Study 1, participants learned to associate one of two Gabor patches (the CS_{LOW}) with lower, and the other Gabor patch cue with higher pain (CS_{HIGH}). During generalization they again received pain preceded by novel Gabor patches with orientations between and beyond the original learning cues.

Methods: Study 2

Participants—As reported in Koban and Wager (2016), 60 healthy volunteers completed the experiment (33 female, mean age = 23.0). All participants were free of psychiatric, neurological, and pain conditions. Each participant signed a written consent form and was paid at the conclusion of the experiment. The University of Colorado Institutional Review Board approved the study.

Stimuli—Learning and generalization stimuli for this task were identical to those in Experiment 1 (see Fig. 1). In addition, social information, i.e. pain ratings of ten other, fictive participants, were presented as vertical bars on a visual analog scale. These social ratings were either low or high on average and were presented at the same time with the learning cues, either above or below the learning cues (randomized across trials). Importantly, this social information was not predictive of actual stimulus intensity and completely orthogonal (independent) of the learning cues (CS_{LOW} and CS_{HIGH}). Please see Koban and Wager (2016) for more details. Yet, as this social information might have potentially altered the strength of cue learning, this design also allowed us to test the generalization effect in a slightly modified experimental context.

Procedures—Procedures in Experiment 2 were mostly identical to Experiment 1. However, instead of five blocks of learning and generalization task, the learning task consisted of six blocks (corresponding to six skin sites chosen in random order and 96 trials in total), whereas the generalization task consisted of only four blocks (corresponding to four different skin sites and a total of 44 trials). All other procedures and analyses of SCR and behavioral data were identical to those in Experiment 1.

Results: Study 2

Learning Task—Pain rating and psychophysiological results for the learning phase have been reported elsewhere (Koban & Wager, 2016). In brief, pain ratings increased as a

function of temperature, $t(37) = 20.46$, $p < 0.001$, Cohen's $d = 2.64$. Further, participants learned to expect more pain for the CS_{HIGH} ($M=55.2$, $STD=11.6$) compared to the CS_{LOW} ($M=50.4$, $STD=11.3$), $t(59) = 4.9$, $p < 0.001$, Cohen's $d = 0.63$ (Fig 3A), and rated pain as higher when preceded by the CS_{HIGH} ($M=55.7$, $STD=13.6$) compared to the CS_{LOW} ($M=53.1$, $STD=13.6$), $t(59) = 3.7$, $p < 0.001$, Cohen's $d = 0.48$ (see Fig. 3B). SCR to pain stimuli preceded by the CS_{HIGH} ($M=1.02$, $STD=0.78$) were only numerically higher than the CS_{LOW} ($M=0.97$, $STD=0.78$), $t(59) = 1.2$, $p = 0.24$ (see Koban and Wager, 2016, for more information and mediation analyses showing that expectations fully mediated the effects of CS on pain reports and SCR).

Generalization Task—In line with our hypothesis, during the generalization phase, we observed a significant linear main effect of Gabor angle on pain ratings, $t(59) = 2.27$, $p = 0.027$, Cohen's $d = 0.29$ (Fig. 3C and Supp. Table S2), indicating that participants generalized the learning cue association with pain to novel, but perceptually similar cues. Replicating the finding in Study 1, this generalization effect was again positively modulated by individual differences in cue effects on expectancy during the learning task, $t(59) = 5.87$, $p < 0.001$, Cohen's $d = 0.76$ (illustrated in Fig. 3D). To characterize this effect, we again performed a median split based on cue effects on expectations during learning. Separate contrasts in the two subgroups indicated that Learners showed a generalization effect, $t(29) = 2.90$, $p = 0.007$, Cohen's $d = 0.53$, whereas Non-learners did not, $t(29) = -0.31$, $p = 0.756$ (see Suppl. Fig. S1). In sum, these findings show a clear generalization effect on pain ratings, with higher pain ratings when the novel stimuli were more similar to the previously learnt CS_{HIGH} compared to the CS_{LOW}. This effect was only seen in participants who explicitly learnt the relationship between cues and pain.

In parallel to the behavioral generalization effects, SCR in the generalization phase of Study 2 were significantly modulated by Gabor angle, $t(59) = 2.45$, $p = 0.017$, Cohen's $d = 0.32$ (see Fig. 3D and Supp. Table S3), yet this effect was not significantly modulated by individual differences in learning, $t(58) = 1.12$, $p = 0.27$. This demonstrates that physiological responses to the same medium pain stimulus were increased when the orientation of the preceding Gabor pattern cue was more similar to the previously learnt CS_{HIGH} compared to the CS_{LOW}.

Overview: Study 3

The third study tested learning effects on pain and their later *conceptual generalization*. In contrast to Studies 1 and 2, drawings of an animal and of a vehicle served as CS during the learning phase and we tested their generalization to other *conceptually* related stimuli, i.e., novel drawings, photos, and words of animals and vehicles (see Figure 4).

Methods: Study 3

Participants—36 volunteers with no psychiatric, neurological, and pain conditions took part in the experiment (12 female, mean age = 26.9). All participants provided written informed consent form and were paid at the conclusion of the experiment. The University of Colorado Institutional Review Board approved the study.

Stimuli—One of the three animal drawings (a dog, cow, or horse) and one of the three vehicle drawings (a car, truck, or train) served as CS_{LOW} and CS_{HIGH}, respectively. Thus, during learning, each participant was only exposed to one animal and one vehicle drawing. Assignment of images to CS condition during learning was fully counterbalanced across subjects. As in Studies 1 and 2, during learning, the CS_{LOW} was always followed by low to medium intensity thermal stimulation (47 or 48 °C, 50% each) and the CS_{HIGH} by medium or high intensity thermal stimulation (48 or 49°C, 50% each, Figure 4A).

The generalization task used a completely different, previously not presented set of animal and vehicle drawings, as well as photos, and words (see Figure 4B). Irrespective of the counterbalancing condition during learning, each participant saw all of the 18 generalization stimuli during the generalization phase. This allowed us to test generalization to other exemplars of the same category (e.g., from dog to cow and horse) and to different modalities of visual presentation (e.g., from the conditioned drawing of a dog to another dog drawing, photo, and the word ‘DOG’). Throughout the generalization task, participants received medium temperature heat stimulation (48 °C), identical to those used in the previous two studies.

Procedures—Procedures in Study 3 were parallel to Studies 1 and 2. First, participants underwent five blocks of the learning task (corresponding to five randomly ordered skin sites on their left volar forearm) with sixteen trials per block. Trial structure and timing was identical to Study 1 and 2. The generalization task consisted of five blocks with 18 trials each, corresponding to one presentation of each of the 18 different generalization stimuli per block. Trial structure and timing was again identical to Studies 1 and 2.

Analysis—The recording and analysis of behavioral and psychophysiological data were parallel to Studies 1 and 2.

Results: Study 3

Learning Task—Replicating the findings of the two previous studies, we again found a strong effect of cue on expectation ratings during learning (CS_{HIGH} M=51.8, STD=28.4, CS_{LOW} M=32.0, STD=19.8), $t(35) = 6.55$, $p < 0.001$, Cohen’s $d = 1.09$ (see Fig. 5A). Pain ratings again showed a strong effect of stimulation temperature (see Fig. 5B), $t(35) = 7.91$, $p < 0.001$, Cohen’s $d = 1.32$. For medium temperature trials, pain ratings were again higher for the CS_{HIGH} (M=46.9, STD=26.3) than the CS_{LOW} (M=37.0, STD=23.0), $t(35) = 5.12$, $p < 0.001$, Cohen’s $d = 0.85$ (Fig. 5B). In contrast to the behavioral findings, no significant main effect of cues on pain-evoked SCR was found during the learning phase, $t(35) < 1$.

Generalization Task—Consistent with our hypothesis of conceptual generalization, pain modulation generalized to novel, previously unseen cues from the same conceptual category (i.e., vehicles versus animals). That is, we found a main effect of CS-category (i.e., category of CS_{HIGH} versus category CS_{LOW}) on pain ratings during generalization, $t(35) = 2.16$, $p = 0.038$, Cohen’s $d = 0.36$ (see Fig. 5C and Suppl. Table S4). As in Studies 1 and 2, this effect was again strongly and positively modulated by the strength of the cue effects on expectations during learning, $t(34) = 4.58$, $p < 0.001$, Cohen’s $d = 0.77$ (relationship shown

in Fig. 5D). A median split based on these individual differences in cue-learning demonstrated that again Learners showed a significant effect of CS-category on pain during the generalization task, $t(17) = 2.61$, $p = 0.018$, Cohen's $d = 0.62$, which was not present in Non-learners, $t(17) = 0.49$, $p = 0.63$ (see Suppl. Fig S1). Thus, in line with the findings of the two previous studies, conceptual generalization depended on explicit learning during the conditioning phase. The relationship between learning and generalization effect is displayed in Figure 5C for all subjects. Paralleling to some degree the behavioral findings, SCR showed a trend towards higher responses to CS_{HIGH}-category stimuli, $t(35) = 1.79$, $p = 0.082$, Cohen's $d = 0.30$ and a trend towards modulation by prior explicit learning (cue effects on expectation ratings during learning), $t(34) = 1.73$, $p = 0.094$, Cohen's $d = 0.29$.

To investigate in more detail how generalization depended on the visual modality or the similarity to the learned cues, we analyzed pain ratings in the three generalization modalities (drawings, photos, and words) and for learnt versus novel animal and vehicle concepts separately (see Figure 6). For instance, if a participant was presented with a dog and a car during learning, the generalization dog and car reflected the learnt concept (albeit depicted in a novel different drawing, photo, or as a word), whereas the depictions of cows, horses, trucks, or trains, would present the novel concepts. Across the whole sample of participants, there were no significant interactions between CS-category and modality, or between CS-category and learned-vs-novel (all p 's > 0.20). However, when adding individual differences in explicit learning (cue-effects on expectation ratings during learning) as a covariate, there was a significant three-way interaction between individual differences in learning, learnt versus novel concepts, and CS-category, $F(2,33) = 6.92$, $p = 0.013$, Cohen's $d = 0.90$. In other words, Learners (again based on median-split) showed steeper slopes (CS-category effects) for the learnt concepts than for the novel concepts (see Figure 6), indicating somewhat stronger generalization to other presentations of the learned concept compared to other concepts of the same category. However, when followed-up with a direct comparison among Learners, the difference between high and low CS-category was trending towards significance for both learnt concepts, $t(35) = 1.73$, $p = 0.092$, Cohen's $d = 0.29$, and new concepts, $t(35) = 1.80$, $p = 0.080$, Cohen's $d = 0.30$. Thus, conceptual generalization worked across different presentation modalities and also extended to other concepts of the same category, but potentially as a function of the conceptual similarity to the original CS.

Discussion

Whereas a growing literature suggests that pain is experienced as more intense, when preceded by conditioned stimuli that have previously been associated with high pain, no previous study has investigated how such learned pain modulation generalizes to novel stimuli. In three experiments, we tested generalization of pain modulation as a function of perceptual and conceptual similarity. Our findings are overall very consistent across the three different studies and suggest several novel insights into this process. First, they demonstrate that generalization modulates pain reports and—although somewhat less consistently across studies—SCR to pain. This extends previous findings that have shown generalization of threat responses (Dunsmoor, Prince, Murty, Kragel, & LaBar; Lissek et al., 2008; Vervliet, Iberico, Vervoort, & Baeyens, 2011), fear of movement-related pain (e.g., Meulders & Vlaeyen, 2013), and reward learning (Guttman & Kalish, 1956; Kahnt et al.,

2012). Second, generalization was observed for both perceptually and conceptually similar stimuli, suggesting that it cannot be explained purely on the basis of a lack of discrimination between CS and generalization stimuli, but that generalization is an active and conceptual process (Dunsmoor & Paz, 2015). Third, our results very consistently show that generalization depends on explicit learning of the CS-contingency during the learning (conditioning) phase. Only participants who learnt to expect more pain for the CS_{HIGH} compared to the CS_{LOW} during the conditioning phase showed generalization of the pain-modulatory effect later on. This again suggests that generalization—at least in this context—is an active process based on explicit learning and expectations. In the following, we will discuss these findings in further detail.

Previous work has demonstrated generalization of fear learning along perceptual similarity gradients (e.g. Armony, Servan-Schreiber, Romanski, Cohen, & LeDoux, 1997; Dunsmoor et al., 2011; Greenberg, Carlson, Cha, Hajcak, & Mujica-Parodi, 2013a; Lissek et al., 2008; Vervliet, Kindt, Vansteenwegen, & Hermans, 2010), including in the context of fear of pain (Meulders et al., 2017; Meulders, Vandebroek, Vervliet, & Vlaeyen, 2013; Meulders & Vlaeyen, 2013). For instance, people show higher fear of and startle responses to movements that are similar to those previously associated with the delivery of a painful shock (Meulders et al., 2013). Hence, on the one hand, the present findings might not be surprising. Yet, on the other hand, the present results are the first ones to show that not only pain-related fear generalizes, but also its modulatory influence on the experience of the *pain itself*. Thus, they provide a potential mechanism of how learning effects on pain and altered pain experience may transfer to novel but related events and situations.

Interestingly, in Studies 1 and 2, generalization followed a linear gradient—in other words, pain ratings were not highest for the generalization stimuli closest to the CS_{HIGH}, but for those who were at the extreme end of the spectrum of tested stimuli. This is similar to what has previously been described as a ‘peak shift’ in generalization (e.g., Hanson, 1959; Honig & Urcuioli, 1981; Kahnt et al., 2012; Struyf, Iberico, & Vervliet, 2014). Two potential mechanisms could explain this linear generalization effect: first, generalization might be dependent not only to the similarity of the CS_{HIGH}, but also on the dissimilarity to the CS_{LOW}. Alternatively, participants might learn to associate a specific dimension (e.g. steepness of the gradient) with higher pain and thus extrapolate from the learnt stimuli. Note that in contrast to typical fear conditioning experiments, in which the CS+ is paired with shock, whereas the CS– is never paired with shock, in learned pain modulation paradigms such as the present studies, both CS_{HIGH} and CS_{LOW} are paired with heat pain stimulation, albeit of different intensity. Thus, the shape of generalization effects might be slightly different.

The findings of Study 3 further corroborate the notion of generalization as an active and conceptual process, by which people actively ‘extrapolate’ learnt associations to novel objects that are conceptually related to the learnt CS. They are in line with the idea that people do not only mechanically associate specific sensory features with painful or pleasant experiences, but they actively infer higher-order patterns and meaning in such associations (e.g., Mitchell, De Houwer, & Lovibond, 2009). Participants, who explicitly learnt the contingency between CS and pain intensity, showed higher pain ratings for other

presentation modalities of the CS_{HIGH}, such as novel drawings, photos, and words, and—to a slightly smaller extent—to novel exemplars of the same category (e.g., other animals or vehicles). Future research could explore in more detail how pain generalization depends on additional features such as stimulus typicality or conceptual distance, which have been shown to play a role in generalization of fear conditioning (Dunsmoor & Murphy, 2014). Further, specific instructions prior to conditioning, such as describing stimuli either in terms of specific exemplars or in terms of broader categories may lead to different expectations and different types of generalization effects.

The present findings are informative for the understanding of placebo and nocebo effects—i.e. changes in symptoms (such as pain) based on an inert ‘fake’ treatment and the sociomedical context in which treatment takes place (Benedetti, 2014; Büchel, Geuter, Sprenger, & Eippert, 2014; Colloca, Klinger, Flor, & Bingel, 2013; Enck, Bingel, Schedlowski, & Rief, 2013; Wager & Atlas, 2015). Placebo effects are thought to be driven, at least in large part, by learning from previous experiences (e.g., Colloca & Benedetti, 2006; Colloca & Miller, 2011; Colloca, Petrovic, Wager, Ingvar, & Benedetti, 2010) and the present work suggests that generalization could explain placebo and nocebo effects also in unconditioned, but perceptually and conceptually similar situations (such as a previously unfamiliar doctor, who also wears a white coat and a stethoscope). Future research could build on the present work by further investigating how instructions, conceptual associations, and generalization interact to form placebo or nocebo responses.

How people learn about pain and generalize those learning experiences also has clinical implications. Research on generalization of fear conditioning suggests that more anxious individuals generalize to a larger degree, i.e. they show broader generalization curves (e.g., Dunsmoor & Paz, 2015; El-Bar, Laufer, Yoran-Hegesh, & Paz, 2016; Greenberg, Carlson, Cha, Hajcak, & Mujica-Parodi, 2013b; Laufer, Israeli, & Paz, 2016; Lissek et al., 2014; Lissek et al., 2010; Schechtman, Laufer, & Paz, 2010). Thus, overgeneralization has been proposed as a maintaining factor in anxiety disorders such as panic disorder, generalized anxiety disorder, and related conditions (Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015; Lissek et al., 2010). Alterations in perceptual discrimination, learning, and generalization may also be important for the development or maintenance of chronic pain (Zaman, Vlaeyen, Van Oudenhove, Wiech, & Van Diest, 2015). A recent study (Meulders, Jans, & Vlaeyen, 2015) investigated generalization of movement-related fear of pain in patients with fibromyalgia—a chronic widespread pain condition—and showed overgeneralization of pain-related fear compared to healthy controls. An interesting possibility for future studies would be to test whether this overgeneralization of fear and avoidance in chronic pain and anxiety conditions also translates to overgeneralization of pain itself, i.e., to a broadening of learned pain responses, which may explain the spreading of chronic pain across different movements or body sites.

A few limitations of the present study should be noted. First, the SCR responses to pain were less consistent across studies than the behavioral effects, i.e. they did not show generalization effects or their modulation by learning across all three studies. The absence of strong effects could be due to a lack of power, as SCR to pain are noisier and habituate much faster than self-report ratings. Habituation in SCR might be especially important, since the

generalization phase only happened after several blocks of learning, in which heat pain stimulation was already administered to the same skin sites. Alternatively, skin conductance responses to pain may follow a slightly different pattern during learning and generalization than self-report pain ratings, for instance by reflecting more implicit aspects of learning (but see Koban & Wager, 2016, for high correlations between self-report and SCR during learning). Further, we did not assess how stimulus representations changed during learning and generalization, and how well participants were able to discriminate the different Gabor patches (Studies 1 and 2). The ability to discriminate different stimuli is a prerequisite for learning and failure to discriminate between different stimuli may also lead to generalization (Struyf, Zaman, Vervliet, & Van Diest, 2015; Zaman et al., 2015). Moreover, previous work has shown sharpening or blurring of tuning curves during fear generalization (e.g., Onat & Büchel, 2015; Resnik, Sobel, & Paz, 2011), which could be relevant in the context of pain as well. Finally, given time constraints and a limited number of trials per condition in Study 3, we did not have sufficient power to address effects of modality and subcategory in more detail. Future studies could extend the present findings in larger samples and use neuroimaging to investigate the neurophysiological mechanisms underlying generalization of learned pain modulation.

Conclusions

In conclusion, our findings across three experimental studies showed that conditioned pain responses generalize to novel, perceptually or conceptually similar cues. Only participants, who were aware of the CS contingency showed this effect. Thus, generalization—at least in the paradigm employed here—seems to depend on the formation of explicit expectations during pain learning and on conceptual processes more broadly. Future studies should investigate how pain generalization is altered in clinical anxiety and in chronic pain conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Megan Powell for help with data acquisition. This research was funded by a SNSF postdoctoral fellowship to LK (PBGE1-142252), an UROP-HHMI fellowship from the University of Colorado Boulder to DK, and NIH grants R01DA035484 and R01MH076136 (TDW).

References

- Amanzio M, Benedetti F. Neuropharmacological Dissection of Placebo Analgesia: Expectation-Activated Opioid Systems versus Conditioning-Activated Specific Subsystems. *The Journal of Neuroscience*. 1999; 19(1):484–494. [PubMed: 9870976]
- Armory JL, Servan-Schreiber D, Romanski LM, Cohen JD, LeDoux JE. Stimulus generalization of fear responses: effects of auditory cortex lesions in a computational model and in rats. *Cerebral Cortex*. 1997; 7(2):157–165. DOI: 10.1093/cercor/7.2.157 [PubMed: 9087823]
- Atlas LY, Bolger N, Lindquist MA, Wager TD. Brain mediators of predictive cue effects on perceived pain. *The Journal of neuroscience*. 2010; 30(39):12964–12977. [PubMed: 20881115]

- Atlas LY, Wager TD. How expectations shape pain. *Neuroscience letters*. 2012; 520(2):140–148. DOI: 10.1016/j.neulet.2012.03.039 [PubMed: 22465136]
- Atlas LY, Whittington RA, Lindquist MA, Wielgosz J, Sonty N, Wager TD. Dissociable influences of opiates and expectations on pain. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2012; 32(23):8053–8064. DOI: 10.1523/JNEUROSCI.0383-12.2012 [PubMed: 22674280]
- Bach DR, Flandin G, Friston KJ, Dolan RJ. Time-series analysis for rapid event-related skin conductance responses. *Journal of neuroscience methods*. 2009; 184(2):224–234. [PubMed: 19686778]
- Bach DR, Flandin G, Friston KJ, Dolan RJ. Modelling event-related skin conductance responses. *International Journal of Psychophysiology*. 2010; 75(3):349–356. [PubMed: 20093150]
- Benedetti F. Placebo effects: from the neurobiological paradigm to translational implications. *Neuron*. 2014; 84(3):623–637. [PubMed: 25442940]
- Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *The Journal of Neuroscience*. 2003; 23(10):4315–4323. [PubMed: 12764120]
- Bennett M, Hermans D, Dymond S, Vervoort E, Baeyens F. From bad to worse: Symbolic equivalence and opposition in fear generalisation. *Cognition and Emotion*. 2015; 29(6):1137–1145. DOI: 10.1080/02699931.2014.973833 [PubMed: 25347279]
- Bennett M, Vervoort E, Boddez Y, Hermans D, Baeyens F. Perceptual and conceptual similarities facilitate the generalization of instructed fear. *Journal of Behavior Therapy and Experimental Psychiatry*. 2015; 48:149–155. DOI: 10.1016/j.jbtep.2015.03.011 [PubMed: 25863485]
- Boddez Y, Bennett MP, Esch Sv, Beckers T. Bending rules: the shape of the perceptual generalisation gradient is sensitive to inference rules. *Cognition and Emotion*. 2016; 0(0):1–9. DOI: 10.1080/02699931.2016.1230541
- Büchel C, Geuter S, Sprenger C, Eippert F. Placebo Analgesia: A Predictive Coding Perspective. *Neuron*. 2014; 81(6):1223–1239. DOI: 10.1016/j.neuron.2014.02.042 [PubMed: 24656247]
- Clark, WC. *Encyclopedia of Neuroscience*. Amsterdam: Elsevier; 2003. Somatosensory and pain measurement by statistical and sensory decision theory.
- Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain Intensity Processing Within the Human Brain: A Bilateral, Distributed Mechanism. *Journal of Neurophysiology*. 1999; 82(4):1934–1943. [PubMed: 10515983]
- Colloca L, Benedetti F. How prior experience shapes placebo analgesia. *Pain*. 2006; 124(1–2):126–133. DOI: 10.1016/j.pain.2006.04.005 [PubMed: 16701952]
- Colloca L, Grillon C. Understanding placebo and nocebo responses for pain management. *Current pain and headache reports*. 2014; 18(6):1–7.
- Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: psychological and neurobiological mechanisms. *Pain*. 2013; 154(4):511–514. DOI: 10.1016/j.pain.2013.02.002 [PubMed: 23473783]
- Colloca L, Miller FG. How placebo responses are formed: a learning perspective. *Philosophical transactions of the Royal Society of London Series B, Biological sciences*. 2011; 366(1572):1859–1869. DOI: 10.1098/rstb.2010.0398 [PubMed: 21576143]
- Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F. How the number of learning trials affects placebo and nocebo responses. *PAIN*. 2010; 151(2):430–439. DOI: 10.1016/j.pain.2010.08.007 [PubMed: 20817355]
- Colloca L, Sigaucho M, Benedetti F. The role of learning in nocebo and placebo effects. *PAIN*. 2008; 136(1–2):211–218. DOI: 10.1016/j.pain.2008.02.006 [PubMed: 18372113]
- Colloca L, Tinazzi M, Recchia S, Le Pera D, Fiaschi A, Benedetti F, Valeriani M. Learning potentiates neurophysiological and behavioral placebo analgesic responses. *Pain*. 2008; 139(2):306–314. DOI: 10.1016/j.pain.2008.04.021 [PubMed: 18538928]
- Dunsmoor JE, LaBar KS. Brain activity associated with omission of an aversive event reveals the effects of fear learning and generalization. *Neurobiology of learning and memory*. 2012; 97(3):301–312. DOI: 10.1016/j.nlm.2012.02.003 [PubMed: 22387662]
- Dunsmoor JE, Murphy GL. Stimulus typicality determines how broadly fear is generalized. *Psychological science*. 2014; 25(9):1816–1821. [PubMed: 25015685]

- Dunsmoor JE, Murphy GL. Categories, concepts, and conditioning: how humans generalize fear. *Trends in cognitive sciences*. 2015; 19(2):73–77. [PubMed: 25577706]
- Dunsmoor JE, Paz R. Fear generalization and anxiety: behavioral and neural mechanisms. *Biological psychiatry*. 2015; 78(5):336–343. [PubMed: 25981173]
- Dunsmoor JE, Prince SE, Murty VP, Kragel PA, LaBar KS. Neurobehavioral mechanisms of human fear generalization. *NeuroImage*. 2011; 55(4):1878–1888. DOI: 10.1016/j.neuroimage.2011.01.041 [PubMed: 21256233]
- Dymond S, Dunsmoor JE, Vervliet B, Roche B, Hermans D. Fear generalization in humans: systematic review and implications for anxiety disorder research. *Behavior therapy*. 2015; 46(5):561–582. [PubMed: 26459838]
- El-Bar N, Laufer O, Yoran-Hegesh R, Paz R. Over-generalization in youth with anxiety disorders. *Social neuroscience*. 2016:1–10.
- Enck P, Bingel U, Schedlowski M, Rief W. The placebo response in medicine: minimize, maximize or personalize? *Nature Reviews Drug Discovery*. 2013; 12(3):191–204. DOI: 10.1038/nrd3923 [PubMed: 23449306]
- Greenberg T, Carlson JM, Cha J, Hajcak G, Mujica-Parodi LR. Neural reactivity tracks fear generalization gradients. *Biological psychology*. 2013a; 92(1):2–8. DOI: 10.1016/j.biopsycho.2011.12.007 [PubMed: 22200657]
- Greenberg T, Carlson JM, Cha J, Hajcak G, Mujica-Parodi LR. Ventromedial prefrontal cortex reactivity is altered in generalized anxiety disorder during fear generalization. *Depression and anxiety*. 2013b; 30(3):242–250. [PubMed: 23139148]
- Guttman N, Kalish HI. Discriminability and stimulus generalization. *Journal of experimental psychology*. 1956; 51(1)
- Hanson HM. Effects of discrimination training on stimulus generalization. *Journal of Experimental Psychology*. 1959; 58(5):321–334. DOI: 10.1037/h0042606 [PubMed: 13851902]
- Harvie DS, Meulders A, Madden VJ, Hillier SL, Peto DK, Brinkworth R, Moseley GL. When touch predicts pain: predictive tactile cues modulate perceived intensity of painful stimulation independent of expectancy. *Scandinavian Journal of Pain*. 2016; 11:11–18. [PubMed: 28850448]
- Hofmann W, De Houwer J, Perugini M, Baeyens F, Crombez G. Evaluative conditioning in humans: a meta-analysis. *Psychological bulletin*. 2010; 136(3):390. [PubMed: 20438144]
- Honig WK, Urcuioli PJ. The legacy of Guttman and Kalish (1956): 25 years of research on stimulus generalization. *Journal of the experimental analysis of behavior*. 1981; 36(3):405–445. [PubMed: 16812256]
- Jensen KB, Kaptchuk TJ, Chen X, Kirsch I, Ingvar M, Gollub RL, Kong J. A neural mechanism for nonconscious activation of conditioned placebo and nocebo responses. *Cerebral Cortex*. 2014:bhu275.
- Jensen KB, Kaptchuk TJ, Kirsch I, Raicek J, Lindstrom KM, Berna C, ... Kong J. Nonconscious activation of placebo and nocebo pain responses. *Proceedings of the National Academy of Sciences*. 2012; 109(39):15959–15964.
- Jepma M, Wager TD. Conceptual Conditioning Mechanisms Mediating Conditioning Effects on Pain. *Psychological science*. 2015; 26(11):1728–1739. [PubMed: 26381506]
- Kahnt T, Park SQ, Burke CJ, Tobler PN. How glitter relates to gold: similarity-dependent reward prediction errors in the human striatum. *The Journal of Neuroscience*. 2012; 32(46):16521–16529. [PubMed: 23152634]
- Kirsch I. Conditioning, expectancy, and the placebo effect: comment on Stewart-Williams and Podd (2004). *Psychological Bulletin*. 2004; 130(2):341–343. discussion 344–345. DOI: 10.1037/0033-2909.130.2.341 [PubMed: 14979776]
- Koban L, Wager TD. Beyond conformity: Social influences on pain reports and physiology. *Emotion*. 2016; 16(1):24. [PubMed: 26322566]
- Krishnan A, Woo CW, Chang LJ, Ruzic L, Gu X, López-Solà M, ... Wager TD. Somatic and vicarious pain are represented by dissociable multivariate brain patterns. *Elife*. 2016; 5:e15166. [PubMed: 27296895]
- Laufer O, Israeli D, Paz R. Behavioral and Neural Mechanisms of Overgeneralization in Anxiety. *Current Biology*. 2016; 26(6):713–722. [PubMed: 26948881]

- Lissek S, Biggs AL, Rabin SJ, Cornwell BR, Alvarez RP, Pine DS, Grillon C. Generalization of conditioned fear-potentiated startle in humans: experimental validation and clinical relevance. *Behaviour research and therapy*. 2008; 46(5):678–687. [PubMed: 18394587]
- Lissek S, Kaczkurkin AN, Rabin S, Geraci M, Pine DS, Grillon C. Generalized anxiety disorder is associated with overgeneralization of classically conditioned fear. *Biological psychiatry*. 2014; 75(11):909–915. [PubMed: 24001473]
- Lissek S, Rabin S, Heller RE, Lukenbaugh D, Geraci M, Pine DS, Grillon C. Overgeneralization of conditioned fear as a pathogenic marker of panic disorder. *American Journal of Psychiatry*. 2010
- Lovibond PF, Shanks DR. The role of awareness in Pavlovian conditioning: empirical evidence and theoretical implications. *Journal of Experimental Psychology: Animal Behavior Processes*. 2002; 28(1):3. [PubMed: 11868231]
- Maltzman I. Orienting in classical conditioning and generalization of the galvanic skin response to words: An overview. *Journal of Experimental Psychology: General*. 1977; 106(2):111. [PubMed: 874424]
- Meulders A, Jans A, Vlaeyen JWS. Differences in pain-related fear acquisition and generalization: an experimental study comparing patients with fibromyalgia and healthy controls. *Pain*. 2015; 156(1): 108–122. [PubMed: 25599307]
- Meulders A, Vandael K, Vlaeyen JWS. Generalization of Pain-Related Fear Based on Conceptual Knowledge. *Behavior Therapy*. 2017; 48(3):295–310. DOI: 10.1016/j.beth.2016.11.014 [PubMed: 28390494]
- Meulders A, Vandeboeck N, Vervliet B, Vlaeyen JWS. Generalization gradients in cued and contextual pain-related fear: an experimental study in healthy participants. *Frontiers in Human Neuroscience*. 2013; :7.doi: 10.3389/fnhum.2013.00345 [PubMed: 23372547]
- Meulders A, Vlaeyen JWS. The acquisition and generalization of cued and contextual pain-related fear: an experimental study using a voluntary movement paradigm. *Pain*. 2013; 154(2):272–282. DOI: 10.1016/j.pain.2012.10.025 [PubMed: 23211100]
- Mitchell CJ, De Houwer J, Lovibond PF. The propositional nature of human associative learning. *Behavioral and Brain Sciences*. 2009; 32(2):183–198. [PubMed: 19386174]
- Montgomery GH, Kirsch I. Classical conditioning and the placebo effect. *Pain*. 1997; 72(1):107–113. [PubMed: 9272794]
- Onat S, Büchel C. The neuronal basis of fear generalization in humans. *Nature neuroscience*. 2015
- Pearce JM. A model for stimulus generalization in Pavlovian conditioning. *Psychological review*. 1987; 94(1)
- Rescorla RA. Pavlovian conditioning: It's not what you think it is. *American Psychologist*. 1988; 43(3):151. [PubMed: 3364852]
- Resnik J, Sobel N, Paz R. Auditory aversive learning increases discrimination thresholds. *Nature neuroscience*. 2011; 14(6):791–796. [PubMed: 21552275]
- Rosén A, Yi J, Kirsch I, Kaptchuk TJ, Ingvar M, Jensen KB. Effects of subtle cognitive manipulations on placebo analgesia—An implicit priming study. *European Journal of Pain*. 2016
- Schechtman E, Laufer O, Paz R. Negative valence widens generalization of learning. *The Journal of Neuroscience*. 2010; 30(31):10460–10464. [PubMed: 20685988]
- Struyf D, Iberico C, Vervliet B. Increasing Predictive Estimations Without Further Learning. *Experimental psychology*. 2014
- Struyf D, Zaman J, Vervliet B, Van Diest I. Perceptual discrimination in fear generalization: Mechanistic and clinical implications. *Neuroscience & Biobehavioral Reviews*. 2015; 59:201–207. [PubMed: 26571437]
- Vervliet B, Iberico C, Vervoort E, Baeyens F. Generalization gradients in human predictive learning: Effects of discrimination training and within-subjects testing. *Learning and Motivation*. 2011; 42(3):210–220. DOI: 10.1016/j.lmot.2011.03.004
- Vervliet B, Kindt M, Vansteenwegen D, Hermans D. Fear generalization in humans: impact of verbal instructions. *Behaviour research and therapy*. 2010; 48(1):38–43. [PubMed: 19781690]
- Voudouris NJ, Peck CL, Coleman G. The role of conditioning and verbal expectancy in the placebo response. *Pain*. 1990; 43(1):121–128. [PubMed: 2277714]

- Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. *Nature Reviews Neuroscience*. 2015; 16(7):403–418. [PubMed: 26087681]
- Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-Based Neurologic Signature of Physical Pain. *New England Journal of Medicine*. 2013; 368(15):1388–1397. DOI: 10.1056/NEJMoa1204471 [PubMed: 23574118]
- Zaman J, Vlaeyen JWS, Van Oudenhove L, Wiech K, Van Diest I. Associative fear learning and perceptual discrimination: a perceptual pathway in the development of chronic pain. *Neuroscience & Biobehavioral Reviews*. 2015; 51:118–125. [PubMed: 25603316]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Highlights

- Placebo effects on pain are influenced by learning (conditioning) and instructions
- Here we investigate generalization of learned pain modulation to novel stimuli
- Our results show generalization based on perceptual and conceptual similarity
- Generalization effects on pain depend on the strength of learned expectations

A Learning **B Generalization** **Figure 1. Stimuli and experimental design in Studies 1 and 2**

A) During learning, participants learned to associate one Gabor patch (CS_{LOW}) with low to medium heat pain stimulation, and the other patch (CS_{HIGH}) with medium to high heat pain stimulation. Assignment of angle to CS condition was counterbalanced across participants.

B) In the generalization phase, participants were presented with novel Gabor patches, which had angles between and beyond the original learning cues. After the generalization cue, participants received a short heat pain stimulation to the left volar forearm, and then rated how much pain they felt after a short jittered waiting period.

Figure 2. Results of Study 1 (N=38)

A) Pain expectation ratings during the learning task were greater for CS_{HIGH} and CS_{LOW}. B) Pain ratings during the learning task showed a significant modulation by temperature and a significant difference between CS_{HIGH} and CS_{LOW} for the medium intensity stimulation (48°C). C) Pain ratings during the generalization phase. Note that the angles of the original CS (35° and 55°) were not presented during the generalization phase. D) Scatter plot illustrating individual differences in explicit learning and generalization. The stronger participants learned to associate the CS during learning with higher expectations of pain, the steeper was their generalization effect of the learned pain modulation (higher beta) during the generalization phase, i.e. they reported higher pain when the generalization cues were more similar to the CS_{HIGH} than to the CS_{LOW}. E) Skin conductance responses during the generalization phase for different bins of generalization conditions (angles of Gabor patches).

Figure 3. Results of Study 2 (N=60)

A) As in Study 1, pain expectation ratings during learning were higher in CS_{HIGH} than in CS_{LOW} trials. B) Pain ratings during the learning task showed a significant effect of temperature and a significant difference between CS_{HIGH} and CS_{LOW} for the medium intensity stimulation (48°C). C) Significant modulation of pain ratings by similarity to the CS's during the generalization phase. Note that the angles of the original CS (35° and 55°) were not presented during the generalization phase. D) Scatter plot illustrating individual differences in explicit learning and generalization. E) Significant modulation of skin conductance responses during the generalization phase for different bins of generalization conditions (angles of Gabor patches).

A Learning **B Generalization**

Figure 4. Stimuli and experimental design in Study 3 (N=36)

A) During learning, participants were presented with two drawings, depicting one animal (i.e., a dog, a cow, or a horse) and one vehicle (a car, a truck, or a train), that were associated with low to medium (CS_{LOW}) or medium to high heat pain stimulation (CS_{HIGH}), respectively. Assignment of the two drawings was fully counter-balanced across participants. B) In the subsequent generalization phase, we tested conceptual generalization, by presenting 18 novel stimuli, that were again depicting animals or vehicles in three different visual form of presentations: novel drawings, headshot photographs, and words. Note that

each participant only saw one animal and one vehicle during learning, thus the other two types of animal or vehicle were novel, but conceptually related (as members of the same broader categories). In parallel to the procedure in Studies 1 and 2, each trial started with the presentation of a cue, followed by a short heat pain stimulation. After a short jittered waiting period, participants rated how much pain they felt.

Figure 5. Results of Study 3 (N=36)

A) As in the first two studies, pain expectation ratings during learning were higher in CS_{HIGH} than in CS_{LOW} trials. B) Pain ratings during the learning task showed again significant effects of temperature and of CS_{HIGH} versus CS_{LOW} (for the medium intensity stimulation, 48°C). C) Modulation of pain ratings by the category of the generalization stimuli (category of CS_{LOW} versus category of CS_{HIGH}). Vertical bars reflect SEM. D) Scatter plot illustrating individual differences in explicit learning and generalization, again showing a strong relationship between strength of explicit expectations and generalization. E) Skin conductance responses during the generalization phase for pain stimulation preceded by CS_{LOW} versus CS_{HIGH} category stimuli.

Figure 6. Generalization across subcategories and presentation modalities (Study 3, N=36)

A) 'Learners' showed somewhat stronger generalization for the learned CS concepts (dark solid lines, e.g., 'dog' as CS_{LOW} and 'car' as CS_{HIGH}), compared to novel concepts from the same category as the CS (gray dashed lines, e.g., 'cow', 'horse' in the CS_{LOW} category, 'truck' and 'train' in the CS_{HIGH} category), across the three modalities of visual presentation (panels from left to right show CS-category effects for drawings, photos, and words). B) 'Nonlearners' did not show any differences in pain ratings for CS-category for learned or novel concepts, in any modality (drawings, photos, and words). Vertical bars reflect SEM.