Learning Effects on Pain Generalize to Perceptually and Conceptually Similar Cues and Modify Pain Perception

Daniel A. Kusko
University of Colorado, Boulder, daku4202@colorado.edu

Follow this and additional works at: https://scholar.colorado.edu/honr_theses
Part of the Cognition and Perception Commons, Cognitive Psychology Commons, and the Other Psychology Commons

Recommended Citation
https://scholar.colorado.edu/honr_theses/1015

This Thesis is brought to you for free and open access by Honors Program at CU Scholar. It has been accepted for inclusion in Undergraduate Honors Theses by an authorized administrator of CU Scholar. For more information, please contact cuscholaradmin@colorado.edu.
Learning Effects on Pain Generalize to Perceptually and Conceptually Similar Cues and Modify Pain Perception

Daniel Kusko
Dept. of Psychology and Neuroscience

Defense date: April 5th, 2016

Thesis Advisor:
**Dr. Tor Wager**
Dept. of Psychology and Neuroscience

Committee Members:
**Dr. Heidi Day**
Dept. of Psychology and Neuroscience

**Dr. Ravinder Singh**
Dept. of Molecular, Cellular, and Developmental Biology
Abstract

Prior learning about pain can drive a placebo or nocebo effect in later settings and influence pain more broadly. This up- or down-modulation of pain is influenced by expectations and learning during conditioning. After conditioning, it has been shown that the association between the original conditioned stimulus (CS) and the unconditioned stimulus (UCS) can generalize to novel, but similar stimuli. This is known as generalization, which is seen across humans and non-human animals. The present studies tested the hypothesis that conditioning effects on pain will generalize to similar, but novel stimuli; meaning that pain will be modulated in new situations based on perceptual or conceptual similarity to previous conditioned stimuli. Two studies were conducted with healthy participants (study 1, n=40; study 2, n=36) to test the generalization of pain learning to novel, but perceptually and conceptually similar stimuli, respectively. The results of both studies show that learned conditioned pain modulation generalizes to perceptually and conceptually similar stimuli, and that explicit awareness of the cue-pain relationship was necessary for this effect. These findings provide evidence that pain perception can be modulated by generalization stimuli, which could also play a role in clinical placebo effects.

Keywords: associative learning, pain, generalization, conditioning, placebo


**Introduction**

A placebo is an inert substance or form of treatment that produces beneficial therapeutic effects. The placebo response is partly due to how people learn through past experiences in a therapeutic or clinical setting, is strongly influenced by prior conditioning, which can persist over several days (Colloca & Benedetii, 2006). The placebo acts as a signal along with other cues (context, setting, white lab coat, etc.) to form a placebo or nocebo response (Colloca & Miller, 2011). It is possible that these cues generalize to other similar cues to induce more or less therapeutic benefit. Generalization is: “The transfer of an improvement achieved through training to other stimuli. The improvement generalizes to the new stimuli” (Fahle, 2005). Generalization could possibly spread the placebo or nocebo effect after conditioning/learning what is beneficial or not. If someone has found relief from receiving treatment from a doctor or pill, then that expectation of relief could occur after treatment from a nurse, a similar looking pill or another healing situation.

![Diagram of psychosocial context](image)
Figure 1. This diagram shows how placebo responses are formed from a learning perspective. Environmental cues are interpreted by the brain to form expectations and influence behavioral outcomes (Colloca & Miller, 2011).

The figure above shows the different kinds of context cues that contribute to a placebo or nocebo effect. After learning that certain indices are associated with a certain type of therapeutic benefit or injury (conditioning), it is possible to generalize that effect to cues that have never been learned before (Lissek et. al, 2008). Therefore, this research is crucial to understanding what kinds of cues promote generalization. Specifically, how pain can be modulated by previously not reinforced stimuli into being perceived as more or less painful?

Previous research on pain has found that learning associations to conditioned stimuli can modify the perception of pain. That is, prior experiences that pair stimuli with intense pain become more painful, and stimuli paired with lower pain become less painful (Price et. al 2008; Colloca et. al 2010; Atlas et. al 2010). There appears to be a role of conscious expectations in mediating the effects of conditioned pain modulation. Previous studies have found that conscious expectations strongly mediate the effects of conditioning and suggestion on pain reports (Kirsch, 2004; Koban & Wager, 2016), and this may extend to generalization as well.

A related finding in the conditioning literature is that novel but similar stimuli to the original conditioned stimulus (CS) associated with a specific behavioral reaction (e.g. fear) can be generalized and cause comparable reactions. Most of the generalization literature has focused on how subjects continue to show a fear response to the generalization stimulus (GS) after being conditioned to expect
something painful (e.g. shocks) when presented with the CS+ but not the CS-.

Studies have found that participants generalize fear to stimuli that are perceptually similar to the CS+ and not the CS- (Muelders et. al, 2013; Lissek et. al, 2008). How well subjects generalize to the GS is dependent on the salience of the accompanying unconditioned stimulus (UCS) and can be strongly influenced by verbal instructions (Vervliet et. al, 2010).

It is important to define learning in humans and across species to further understand what it means to learn. In this case, *contingency awareness* may be necessary to learn which visual stimuli are associated with different levels of pain. *Contingency awareness* is defined as: “knowledge that a specific CS predicts a specific US (“the tone predicts shock”)” and is thought of as a link between animal and human conditioning models (Lovibond & Shanks, 2002). Learning associations to certain stimuli though conditioning can then generalize to novel, but similar stimuli. Across species, both learning and generalization have been observed. Honeybees can be trained to learn associations between an odor stimulus (CS) and receiving sucrose (UCS). They show a generalized response to novel odors that are perceptually similar to the original CS (Smith, 1993). Similar responses of perceptual generalization have also been found for humans, pigeons, and rats (Maes, et. al, 2015; Dunsmoor & Murphy, 2015). Therefore, generalization is ubiquitous in organisms and is observed after associative learning. This implies that it is an adaptive tool for survival.

However, perceptual similarity to the original conditioned stimuli is not the only way of generalization. Generalization of conditioned fear can occur through
conceptual knowledge of objects (Dunsmoor & Labar, 2012). This can happen after participants undergo a category-based conditioning paradigm (Dunsmoor & Murphy, 2014). These two studies show that conceptual structures are important for the generalization of fear even when physical similarity between the original CS and the new generalization stimuli (GS) is highly variable. For example, someone bitten by a dog might later generalize his or her fear to perceptually similar stimuli (other dogs). Their fear of dogs might also generalize to the concept of a dog and would show a fear reaction to someone saying the word “dog”. It is important to untangle the differences between perceptually similar generalization and conceptually similar generalization because one or both of these effects might modulate placebo responses. So far, no other studies have looked at whether pain perception can be modulated by previously not conditioned generalization stimuli.

It is possible that generalization of pain would also occur in a similar fashion as the generalization of fear. That is, the generalization cues closer in similarity to the CS+ would elicit more pain and the generalization cues closer in similarity to the CS- would result in less pain. Therefore, the aim of investigation includes: (a) can perceptually similar cues modulate pain perception? (b) Can conceptually similar cues modulate pain perception? And (c) does such generalization of conditioned pain modulation depend on explicit learning of the cue-pain relationship? Two studies were conducted to investigate if learning effects on pain generalize to similar cues and modify pain perception.

The first experiment was designed to test generalization of pain to perceptually similar cues. This was done by conditioning participants to expect
different levels of pain based on the angle of lines in two abstract images (Gabor patch, see methods). Then, they were presented with eleven different angles of similar Gabor patches, and given identical thermal pain stimulation, to test if their previous association to angle and pain generalized to the new images. The second was used to test generalization of pain to conceptually similar cues. The experimental design was similar to the previous experiment but instead of Gabor patches at different angles, participants saw pictures of animals and vehicles. Generalization of pain was tested again by showing eighteen conceptually similar pictures while participants received identical thermal pain stimulation.

Methods (Study 1)

Overview
This study sought to test learning (conditioned cue) effects on pain and their generalization to perceptually similar stimuli. We hypothesize that pain will be perceived as lower when preceded by a low cue (Gabor angle 35°) and higher when pain is preceded by a high cue (Gabor angle 55°). We also predict that later presentation of heat stimulation will be perceived as more painful when preceded by gradients that were more similar to the CShigh (higher angles). Lastly, we hypothesize that generalization will only occur for participants who are explicitly aware of the cue-pain relationship.

Participants
38 healthy volunteers took part in the experiment (16 female, age range: 18 – 55, mean age = 26.6). All participants underwent a screening process to guarantee
they were free of psychiatric, neurological, and pain conditions. One additional participant did not complete the task due to high pain sensitivity. 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.

**Materials and Procedures**

**Stimuli.** Participants were informed before the first task that they would see one of two abstract images (Gabor patches) before the application of heat pain (Gaussian envelopes (www.cogsci.nl/software/online-gabor-patch-generator). One image was a Gabor patch with the orientation angle at 35 degrees and another with an orientation angle of 55 degrees. Participants were partially reinforced to expect higher or lower heat pain depending on the preceding cue. One of the Gabor patches (Cue\textsubscript{LOW}) was followed by low to medium intensity thermal stimulation (47 or 48 °C) and the other Gabor patch (Cue\textsubscript{HIGH}) was followed by medium or high intensity thermal stimulation (48 or 49 °C). The assignment of Gabor patches to CS\textsubscript{LOW} and CS\textsubscript{HIGH} was counterbalanced across participants. The generalization task used a different set of Gabor patches with orientation angles at 25°, 29°, 33°, 37°, 41°, 45°, 49°, 53°, 57°, 61°, and 65° followed by medium intensity thermal stimulation (48 °C).

Heat pain stimulation was 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). Baseline temperature was set to 32°C. Heat pain stimulation was presented in short durations with 40°C/s ramp rate and 1s plateau at target temperatures.
Pain Learning and Generalization

**Procedures.**

*Calibration*

Participants first performed a brief calibration procedure (total of 15 trials at all 5 skin sites, temperatures ranged from 44 - 50°C). This was used to test their individual sensitivity to pain and to get them accustomed to the type of heat pain stimulation. They were asked to make their pain ratings on a horizontal visual analog scale.

*Learning Phase*

Next, they were instructed that we were interested in their perception of pain and how well they could estimate the pain in the upcoming trial based on one of two “abstract pattern” cues. Participants were informed that one cue was followed by higher pain and the other cue was followed by lower pain on average. Then, participants underwent five blocks of the learning task with sixteen trials per block. Each block tested a different skin site in randomized order. At the beginning of each trial, subjects were presented with one of two predictive Gabor patches (Cue_LOW or Cue_HIGH) for 4 seconds. After the visual cue, participants were asked to rate how much pain they expected to receive using a horizontal visual analog scale (expectation rating). Participants were then stimulated with low (47°C, 25% of trials), medium (48°C, 50% of trials), or high (49°C, 25% of trials) heat pain. After a jittered 3-5s delay, they were asked to rate how much pain they actually felt, again using a horizontal visual analog scale (pain rating). The inter trial interval had a jittered duration of 6.5-9s.
**Pain Learning Task:**

![Diagram of Pain Learning Task]

**Figure 2.** Experimental design for the learning task. Participants were presented with one of two Gabor patches with different orientation (35° and 55° angle). One Gabor patch (CSLOW) was followed by low-to-medium (47 or 48°C), the other Gabor patch (CSHIGH) with medium-to-high (48 or 49°C) heat stimulation. Following the image, participants had to make a pain expectation rating on a visual analog scale. Then, they received a 1 second heat stimulation on their left volar forearm and rated the pain intensity on a visual analog scale.

**Generalization Phase**

After the learning task, participants took part in a generalization task to test whether the learned associations from the previous task generalized to new but perceptually similar cues. Participants were presented with one of the eleven generalization stimuli (4s) and asked to rate their pain after receiving heat stimulation which was 48°C for all 55 trials (11 trails per random skin site). Participants rated their pain on a horizontal visual analog scale (pain rating) after a jittered (3.5 to 6.5s) wait screen. The inter-trial interval (ITI) was a jittered length between 5.5-8s.
**Generalization Task:**

*Figure 3.* Experimental design for the generalization task. Participants were presented with new Gabor patches, that had an orientation ranging from 25° to 65° angles. The orientation angles ranged between and beyond the CS low and CS high but did not include them. Participants received 1-second medium heat stimulation and asked to rate the pain intensity on a visual analog scale.

**Other Measures.** All participants completed a series of questionnaires to determine their state and trait level of various personality factors which have been implicated in individual placebo response (Wager, et. al, 2011). We assessed each participant’s state and trait anxiety using the STAI-S and STAI-T (Reed, et. al, 1991), as well as pain-related anxiety using the Fear of Pain questionnaire (McCraeken, et. al, 1992).

Previous research to uncover what personality factors contribute to the placebo effect has found that trait optimism (Morton et. al, 2009) and behavioral activation (Leknes & Tracey, 2009) are good predictors for placebo responders. To assess how these personality factors contribute to different aspects of the placebo effect (learning, expectations, and verbal instructions) we measured participant’s behavioral activation/inhibition using the BIS/BAS scale (Carver & White, 1994)
and the LOT-R questionnaire for trait optimism (Scheier, et. al, 1994).

In addition, we included questionnaires measuring empathy and social desirability to test whether these factors affected the learning and perception of pain under verbal instructions. Empathy was measured using the Interpersonal Reactivity Index (Davis, 1980), while Social desirability was assessed using the Social Desirability Scale (Crowne & Marlowe, 1960).

**Analysis**

Behavioral ratings were acquired on visual analog scales 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 to test how learning cues affected pain expectation ratings, across all trials, and pain ratings for medium temperature trials (48°C) to control for temperature.

A multi-level mediation analysis (Kenny, et. al, 2003; Krull & MacKinnon, 2001) was used to test whether the effects of learning cues (CueHIGH versus CueLOW) were mediated by trial-wise and subject-wise differences in pain expectancy. The code for the multi-level GLM and the M3 multi-level mediation toolbox are available at wagerlab.colorado.edu/tools. Other statistical analyses were conducted in Matlab. A significance level of $p < 0.05$ was applied to all analyses unless indicated otherwise.

**Methods (Study 2)**
Overview

This study sought to test whether conditioned cue effects on pain can generalize to conceptually similar novel stimuli. We hypothesize that pain will be perceived as lower when preceded by a conditioned low cue (e.g., cartoon dog) and higher when pain is preceded by a conditioned high cue (e.g., cartoon car). We also predict that later presentation of heat stimulation will be perceived as more painful when preceded by images or representations of conceptually similar objects (e.g., other vehicles, as compared to other animals). Lastly, we hypothesize that generalization will only occur for participants who are explicitly aware of the cue-pain relationship.

Participants

36 healthy volunteers took part in the experiment (12 female, age range: 18 – 55, mean age = 26.9). All participants underwent a screening process to guarantee they 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.

Materials and Procedures

Stimuli. Participants were informed before the first task that they would see one of two pictures (cartoon animal or cartoon vehicle) before the application of heat pain. Participants saw one of the three animal pictures and one of the three vehicle pictures (see below). Participants were partially reinforced to expect higher or lower heat pain depending on the preceding cue. Assignment of images (animal or vehicle to $\text{Cue}_{\text{Low}}$ or $\text{Cue}_{\text{High}}$) during learning was counterbalanced across subjects. One of the pictures ($\text{Cue}_{\text{LOW}}$) was followed by low to medium intensity thermal
stimulation (47 or 48 °C) and the other picture (Cue_{HIGH}) was followed by medium or high intensity thermal stimulation (48 or 49 °C).

**Figure 4.** Learning task stimuli. Participants saw one of the three animal cues and one of the three vehicle cues.

The generalization task used a different, previously not presented set of animal and vehicle images (see below). For each cartoon image used in the last task there were three variations corresponding to the previous pictures (18 generalization stimuli). Throughout this task, participants received medium temperature heat stimulation (48 °C).

**Figure 5.** Generalization stimuli. All participants saw 18 generalization stimuli during this phase.

Heat pain stimulation was 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). Baseline temperature was set to 32°C. Heat pain stimulation was presented in short durations with 40°C/s ramp rate and 1s plateau at target temperatures.

**Procedures**
The overall procedures in Study 2 were the same as in Study 1, except different types of visual stimuli were used. Heart rate and skin conductance measures were taken throughout the two tasks, but the results will not be presented. After both tasks, physiological recordings were stopped and participants made various ratings on the pictures they saw (similarity and other ratings – see below).

**Learning Phase**

Participants underwent five blocks of the learning task with sixteen trials per block. Each block tested a different skin site in randomized order. At the beginning of each trial, subjects were presented with one of two predictive pictures \( \text{Cue}_{\text{LOW}} \) and \( \text{Cue}_{\text{HIGH}} \) for 4 seconds. After the visual cue, participants were asked to rate how much pain they expected to receive using a horizontal visual analog scale (expectation rating). Participants were then stimulated with low (47°C, 25% of trials), medium (48°C, 50% of trials), or high (49°C, 25% of trials) heat pain. After a jittered 3-5s delay, they were asked to rate how much pain they actually felt, again using a horizontal visual analog scale (pain rating). The inter trial interval had a jittered duration of 6.5-9s.
**Pain Learning Task:**

![Diagram of Pain Learning Task]

**CS\_LOW** (47°C, 48°C) **CS\_HIGH** (48°C, 49°C)

**Figure 6.** Experimental design for the learning task. Participants were presented with one of two animal or vehicle pictures. One image (CS\_LOW) was followed by low-to-medium (47 or 48°C), the other image (CS\_HIGH) with medium-to-high (48 or 49°C) heat stimulation. Following the image, participants had to make a pain expectation rating on a visual analog scale. Then, they received a 1 second heat stimulation on their left volar forearm and rated the pain intensity on a visual analog scale.

**Generalization Phase**

After the learning task, participants took part in a generalization task to test whether the learned associations from the previous task generalized to new but conceptually similar stimuli. Participants were presented with one of the eighteen generalization stimuli (4s) and asked to rate their pain after receiving heat stimulation which was 48°C for all 90 trials (18 trails per random skin site).

Participants rated their pain on a horizontal visual analog scale (pain rating) after a jittered (3.5 to 6.5s) wait screen. The inter-trial interval (ITI) was a jittered length between 5.5-8s.
Generalization Task:

Figure 7. Experimental design for the generalization task. Participants were presented with new images, which were conceptually related to the learning cues but did not include them. Participants received 1-second medium heat stimulation and asked to rate the pain intensity on a visual analog scale.

Similarity and Other Ratings

Next, participants were presented with images from both the learning phase and the generalization phase. The similarity ratings were used to test how related participants thought two pictures were to each other. We used the other ratings to gauge each participants pre and post experimental attitudes toward the pictures. They rated how related the two images were using a visual analog scale (similarity ratings). Then, they were asked to make other ratings for each image individually using a visual analog scale with a 1 second fixed cross between each question. These ratings were of typicality (how typical is this image?), pain (how much pain do you associate with this image?), valence (how positive or negative is this image?), arousal (how emotionally arousing is this image?), and fear (how much fear does
this image evoke?). Although these ratings were helpful for determining participants’ attitudes toward the images, the results will not be presented.

**Other Measures.** The series of questionnaires used in study 1 were also used to examine individual differences in personality in study 2. However, one survey was added to study 2 to assess the level of pain catastrophizing in each participant. The Pain Catastrophizing Scale (PCS) is a questionnaire used to look at how catastrophizing impacts pain perception (Sullivan, et al, 1995).

**Analysis**

The analysis techniques used were the same as in study 1.

**Results (Study 1)**

**Learning Task**

*Effects of Temperature.* First, we looked at whether participants could discriminate between heat stimulation intensities, and whether pain ratings increased as a function of temperature intensity. A multi-level robust regression (see Methods) found a significant effect of temperature on pain ratings ($t(37) = 12.51, p < .0001$), as shown in Figure 8.
Figure 8. Mean pain ratings by temperature in degrees Celsius. There was a significant effect of temperature on pain ratings across participants.

**Effects of Learning Cues on Pain Ratings.** Next, we examined the effect of the two learning cues on pain ratings for medium temperature intensity (48°C) only. A significant effect of conditioned cues (Cue Low versus Cue High) on pain rating was found, \( t(37) = 3.83, p < .001 \) as shown in Figure 9.
Figure 9. Mean pain ratings by condition. Effect seen for pain ratings between the Cue Low and Cue High conditions for medium temperature (48 degrees Celsius) only.

Cue effects on expectation. Then, we calculated the cue effect on expectation rating during the learning phase. A significant effect of Cue LOW versus Cue HIGH was found for mean expectation ratings \((t(37) = 4.54, p < .001)\), as seen in figure 10, confirming our first hypothesis.
**Figure 10.** Cue effect on mean expectation ratings by time. There was a significant effect of cue on expectation ratings that developed over time.

**Generalization Task**

**Pain Reports.** First, we split the participants by strength of individual learning from the cues in the learning phase. Individual differences were calculated by taking a median split of the 1st level beta values from the cue effect on expectation during learning. During the generalization phase, there was a significant linear effect of Gabor angle on pain ratings, \((t(37) = 3.65, p < .001)\) showing that participants generalized the cue-pain association from the learning task to novel, but perceptually similar cues (Figure 11 (learners)), confirming our second hypothesis. Individual differences in cue effects on expectancy from the learning task also significantly modulated this generalization gradient \((t(18) = 3.74, p < .002)\), indicating that participants who learned to associate the learning cues with pain levels showed a generalization effect. Also, participants who did not learn to
associate the learning cues with pain levels did not show a significant effect of Gabor angle on pain ratings ($t(18) = -0.97, p = .3441$), as shown in Figure 11 (non-learners).

![Pain Ratings Generalization](image)

**Figure 11.** Results from the generalization task. Pain ratings (learners) from the eleven different stimulus angles used in the generalization task, ranging from 25 to 65° orientation (corrected for counterbalancing condition). Stimuli with greater angle, therefore resembling more the CSHIGH (55°) than the CSOLEW (35°) was associated with higher pain ratings than lower-angled generalization cues (significant linear effect). Pain ratings (non learners) from the eleven different stimulus angles used in the generalization task. Not significant linear effect of angle on pain ratings.

**Results (Study 2)**

**Learning task**

*Effect of Temperature.* First, we looked at whether participants could discriminate between heat stimulation intensities, and whether pain ratings increased as a function of temperature intensity. A multi-level robust regression
(see Methods) found a significant effect of temperature on pain ratings ($t(35) = 7.91, p < .0001$), as shown in Figure 12.

![Pain ratings by temperatures](image)

**Figure 12.** Mean pain ratings by temperature in degrees Celsius. There was a significant effect of temperature on pain ratings across participants.

**Effects of learning cues on pain ratings.** Next, we examined the effect of the two learning cues on pain ratings for medium temperature intensity (48° degrees Celsius). A significant effect of conditioned cues (CUE LOW versus CUE HIGH) on pain rating (medium temperature only) was found, ($t(35) = 6.55, p < .0001$) as shown in Figure 13, confirming our first hypothesis.
Figure 13. Mean pain ratings by condition. Effect seen for pain ratings between the Cue Low and Cue High conditions for medium temperature (48°C) only.

Cue effects on expectation. Then, we calculated the cue effect on expectation during the learning phase. A significant effect of CUE LOW versus CUE HIGH was found for mean expectation ratings (\(t(35) = 5.12, p < .0001\)), as seen in figure 14.
Figures 14. Cue effects on mean expectation ratings by time. There was a significant effect of cue on expectation ratings that developed over time.

Generalization Task

Pain Reports. First, we split the participants by strength of individual learning from the cues in the learning phase. Individual differences were calculated by taking a median split of the 1st level beta values from the cue effect on expectation during learning. During the generalization phase, there was a significant effect of conditioned stimulus category on pain ratings, \( t(35) = 2.16, p = .0379 \) showing that participants generalized the cue-pain association from the learning task to novel, but conceptually similar cues, confirming our second hypothesis (Figure 15 (a)). Individual differences in cue effects on expectancy from the learning task also significantly modulated this generalization gradient \( t(17) = 2.61 \ p = .0183 \), indicating that participants who learned to associate the learning cues with pain levels showed a generalization effect (Figure 15 (b)). Also, participants who did not learn to associate the learning cues with pain levels did not show a significant
effect of conditioned stimulus category on pain ratings \((t (17) = .489, p = .6311)\), as shown in Figure 15 (c). Both studies taken together showed a learning effect on generalization, confirming our third hypothesis.

![Figure 15](image)

**Figure 15.** This figure shows the effect of CS Low versus CS high category on pain ratings. (a) Across all participants, there was a significant effect of CS category on pain ratings. Plot (b) shows the CS low versus CS high category effect on pain ratings for learners only. There was a significant effect of CS category on pain ratings for learners. (c) Shows the effect of CS category for non-learners, which is not statistically significant across low versus high CS category.

**Pain reports by learned and new exemplars (Learners only).** Next, we calculated the differences in pain ratings for the learned exemplars and new exemplars for high and low categories. We took data from learners only because they showed a stronger effect of the cues on pain ratings. There was a significant effect between low category new exemplars and high category new exemplars (t
Pain Learning and Generalization

(17)=2.49, p = .0232). There was no significant difference between the new and learned exemplars for both high and low categories. Surprisingly, there was no difference between low category learned exemplars and high category learned exemplars. Visual inspection does suggest that there is an effect of learned exemplars for the high and low categories, but this is not statistically significant.

![Pain rating by learned and new exemplars](image)

**Figure 16.** Mean pain ratings in the generalization phase for low and high learned and new exemplar categories from the learners group.

**Pain reports by sub modality (Learners only).** Then, we calculated the effects for low versus high category sub modalities on pain ratings. We took data from learners only because they showed a stronger effect of the cues on pain ratings. However, only the cartoon sub modalities for high and low cues reached a significant effect (t (17) = 3.36, p = .0037). The word and picture sub modalities did
not show a significant difference between high and low category. Visual inspection shows that there could be an effect of modality on pain but more power would be needed to see a statistically significant difference.

![Pain ratings by sub modality](image)

**Figure 17.** Effect of low and high category sub modalities on mean pain ratings for learners only in the generalization task.

### Discussion

The present findings suggest that learning associations to conditioned cues can modulate pain, and that this learning can generalize to perceptually and conceptually similar novel cues (aims (a) and (b)). Explicit awareness of the cue-pain relationship was also important for the modulation of pain through conditioning and its generalization to novel but similar stimuli (aim (c)). Prior learning experiences in therapeutic or clinical settings play a key role for the
placebo effect. This research provides evidence that prior associations to pain and visual stimuli can generalize to perceptually and conceptually similar visual stimuli. Therefore, it is possible that the placebo effect can generalize to novel situations and modulate pain perception.

Taken together, these findings are important for understanding how prior learning experiences shape placebo and nocebo responses. Previous research on the learning aspect of placebos has found that conditioning, which can then modulate expectations, modulates pain experience (Colloca & Miller, 2011; Kirsh, 2004). Conditioned expectations play a major role in the generation of the placebo effect, along with social interactions, past experiences and individual genetic makeup.

Placebo research has uncovered brain areas responsible for the effect of expectations on pain experience. Specific regions activated during the expectation of pain relief include the anterior cingulate cortex (ACC), pre-frontal cortex (PFC), and the periaqueductal gray (PAG) (Amanzio et. al, 2013). This could imply that there is a network of activation dedicated to modulating pain based on previous expectations. More research needs to be done to determine the how the magnitude of conditioned expectation affects the placebo response.

Previous research examining the underlying neurotransmitters involved in the placebo effect has found oxytocin, dopamine, and opioids as playing an important role. The neuropeptide oxytocin is thought to be influential for the placebo effect. Ahmad Abu-Akel, et. al., (2014) found that an administration of intranasal oxytocin increased the pain relief from a placebo. Another interesting finding is that high placebo responders show increased dopamine and opioid
neurotransmission release from right nucleus accumbens (NA). The dopamine coming from the nucleus accumbens activates the opioid system to modulate pain (Scott, et. al, 2008). Individual differences in dispositional optimism have been shown to affect placebo response (Morton, et. al, 2009). However, none of the personality measures taken during the two studies reached a significant correlation with the learning effects on pain found.

Based on the evidence from both studies, it is clear that pain can also be modulated by generalization stimuli that are perceptually and conceptually similar to previously conditioned cues. Previous research on generalization has found that after conditioning, similar conditioned responses are present for stimuli that are novel, but similar to the original conditioned stimuli (Guttman & Kalish, 1956; Pearce, 1987). Similar results have also been found for the generalization of conditioned fear (Muelders et. al, 2013; Lissek et. al, 2008). Fear generalization can also occur through conceptually similar stimuli after conditioning (Dunsmoor & Labar, 2012; Dunsmoor & Murphy, 2014). However, no previous studies have been done to examine whether pain experience can be modulated by generalization stimuli.

How an organism learns about pain underlies much of the current research looking at the placebo effect. Generalization is an effect seen only after learning and is thought to be an example of higher order Pavlovian conditioning. Recent evidence coming from a study on fear generalization has found neural correlates of this effect. The posterior cingulate cortex (PCC), anterior cingulate (ACC), vmPFC, anterior insula (aIC), hippocampus and inferotemporal cortex (ITC) were all more active
during the fear-tuned response to generalization stimuli (Onat & Büchel, 2015).
Interestingly, aIC activity increased for generalization stimuli closer to the CS+, and decreased for stimuli near the CS- (Face stimuli for CS and shocks used for UCS).
Another critical effect found was that the ITC response differentiated intermediate stimuli from the CS+/-, implying that this area is responsible for encoding ambiguity based uncertainty for fear. Generalization was at first thought to be a failure to discriminate between stimuli, but this research implies that it is an active process of widening the scope of threat to perceptually similar stimuli.

Both studies were designed to test the effects of pain conditioning on later generalization to novel, but similar stimuli. The first study was used to look at the generalization of pain to perceptually similar stimuli using different orientations of Gabor patches. Pain perception was modulated by the degree of perceptual similarity to the original conditioned stimuli. Study 2 also tested the generalization of pain with a similar paradigm, but to conceptually similar stimuli. The results suggest that conceptual similarity to the previously conditioned stimuli promotes the generalization of pain using images of animal and vehicle categories.

The findings from these two studies are also important for understanding PTSD, chronic pain, and anxiety disorders. Overgeneralization of fear and/or pain has been implicated in contributing to the debilitating symptoms of these diseases (Zaman et. al, 2015; Lissek et. al, 2008; Lissek et. al, 2010). The present results find generalization of pain in a healthy population. It is possible that looking at a clinical population with a similar paradigm could show the degree to which patients generalize or overgeneralize conditioned effects on pain.
There are some limitations to both of these studies. Study 2 found generalization of pain to conceptually similar stimuli. However, this effect was not completely independent of perceptual similarity. The transfer of the cue-pain relationship made between animals and vehicles could have transferred to novel, but conceptually similar stimuli partly due to shared physical similarity (e.g. fur, legs, man-made material, etc.). Also, we cannot say anything about the difference in pain ratings across learned exemplars for the high and low category, surprisingly. Also there was no significant difference between high and low category for word and picture sub modalities. Therefore, the super ordinate category of animal and vehicle generalizing was significant but not for sub ordinate categories of words and real life pictures. An experimental design with more power may find more fine-tuned generalization.

Study 1 did not find an effect of generalization on skin-conductance and the physiological data from study 2 has not been analyzed yet. Therefore, the effects of generalization on physiology are still open to debate. An experiment examining the neuronal network of activation associated with the modulation of pain through generalization might lead to interesting results on the underlying emotional, cognitive, and behavioral factors contributing to these effects.

Conclusions

Both studies show novel evidence that perceptual and conceptual similarity to previously conditioned stimuli can modulate pain perception through generalization. These findings are important for understanding how a placebo or nocebo response could be elicited in novel situations through the generalization of
learned cue effects on pain perception. Individual learning during the conditioning procedure drove this effect, implying that explicit awareness of the cue-pain relationship is crucial for the generalization effects on pain. Future research looking at the brain areas implicated in pain generalization will be important for understanding the present findings.

Acknowledgments

I would like to thank UROP HHMI for funding this research. I would also like to thank Leonie Koban for helping with experimental design, analysis, and discussion of results and advice on the write up. I would also like to thank Tor Wager for providing grant funding for all the equipment and materials used to conduct this research, as well as helpful discussion of results and advice for the experimental design.

Works Cited

Ahmad Abu-Akel, Sharon Palgi, Ehud Klein, Jean Decety & Simone Shamay-Tsoory (2015) Oxytocin increases empathy to pain when adopting the other- but not the self-perspective, Social Neuroscience, 10:1, 7-15, DOI: 10.1080/17470919.2014.948637


Dunsmoor, Joseph E., Alex Martin, and Kevin S. LaBar. "Role of conceptual knowledge in learning and retention of conditioned fear." Biological psychology 89.2 (2012): 300-305.


Meuldiers, et al. (2013) “Generalization Gradients in Cued and Contextual Pain-Related Fear: An Experimental Study in Healthy Participants.” *Frontiers in Human Neuroscience*


Pain Learning and Generalization


