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Can placebo and nocebo effects generalize within pain modalities and across somatosensory sensations?

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Abstract: Pain and other somatosensory sensations, such as itch, can be effectively decreased by placebo effects and increased by nocebo effects. There are indications that placebo effects on pain generalize to other sensations and that nocebo effects generalize within itch modalities. However, it has not yet been investigated whether learned effects can generalize within pain stimulus modalities or from pain to itch. Our aims were to test whether placebo and nocebo effects can generalize within pain modalities, i.e., from heat pain to pressure pain, and across somatosensory sensations with psychophysiological similarities, i.e., from heat pain to cowhage-evoked itch. For this purpose, sixty-five healthy participants were randomized to either a placebo or nocebo group. All participants firstly underwent a conditioning and verbal suggestion procedure with heat pain stimuli. Subsequently, responses to heat pain, pressure pain, and cowhage-evoked itch stimuli were tested. Results showed that altered levels of heat and pressure pain with the conditioned cue in both placebo and nocebo groups in the expected directions, but no significant difference in itch in both groups. In conclusion, placebo and nocebo effects on pain may generalize within but not across stimulus modalities. This study provides a novel perspective on the role that response generalization plays in physical symptoms.

Keywords: generalization; placebo; nocebo; conditioning and verbal suggestions; itch

Introduction

Pain and itch are common, debilitating physical symptoms.[6,18,25] They have been found to be sensitive to placebo and nocebo effects,[5,12,21] i.e., beneficial or adverse effects occurring upon administration of an inert treatment or as part of active treatments, due to mechanisms such as expectancies.[10] Knowledge on the mechanisms underlying these effects may offer insights for improving treatment of both pain and itch. A vast body of research shows that expectancies can be shaped by verbal suggestions and classical conditioning.[43] Verbal suggestions evoke expectancies via explicit instruction, e.g., by telling participants that a treatment will relieve pain.[5] Classical conditioning is a type of learning in which a conditioned stimulus (e.g., a cue) is repeatedly paired with an unconditioned stimulus (e.g., low temperatures) that evokes a conditioned response (e.g., less pain), hence inducing expectancies.[10,19]

Past experience plays an important role in placebo and nocebo effects.[11,34] For instance, cues related to a prior learned placebo association may activate expectancies about what might be experienced in the current novel situation. This transferability from prior experience to a new situation, triggered by related cues, is an important adaptive feature of learning called generalization.[16] We can distinguish two different types of this phenomenon: stimulus generalization and response generalization. Stimulus generalization, the most frequently investigated, occurs when a novel stimulus, that is usually similar to the original stimulus, elicits a corresponding response as the originally conditioned stimulus.[16,26,27,29] Less frequently studied is generalization at the response level. This entails that a generalization response alike the initially conditioned response is triggered by a stimulus.[38] For example, when a patient has positive prior pain analgesic experiences from a doctor's treatment, positive treatment outcomes (as well as related expectations) when being treated by the same doctor (serving as a cue) might generalize to other pain symptoms.

Experimental evidence for response generalization within and across stimulus modalities is scarce. To our knowledge, only one study demonstrated that response generalization can occur within modality, i.e., learned nocebo effects may generalize from electrically-induced itch to histaminergic itch.[2] Two studies demonstrated that generalization of placebo effects can occur across stimulus modalities, i.e., from pain to muscle fatigue,[7] and from pain to pain-unrelated negative emotion.[46] So far, it is unknown whether response generalization of learned placebo and nocebo effects on one pain stimulus also affects pain experienced from other pain stimuli. Moreover, despite the commonalities between pain and itch, response generalization of placebo and nocebo effects from pain to itch has never been studied.

The aims of our study were to test the hypotheses that placebo and nocebo effects can generalize 1) within pain stimuli modalities, specifically from heat pain to pressure pain (primary outcome), and 2) across stimulus modalities, specifically from heat pain to cowhage-evoked itch (secondary outcome). To this end, we first induced either placebo or nocebo effects on heat pain in healthy participants via combining verbal suggestion and classical conditioning, and subsequently tested response generalization to pressure pain and itch evoked by cowhage plant particles.

Methods and Materials

Participants

Based on a previous study investigating generalization,[2] a power analysis conducted via G*Power 3.1, indicated that 68 participants would be required in total (both placebo and

nocebo group) for a paired samples t-test with an expected effect size *dz* of 0.5, a two-sided alpha α of 0.05 and a desired power of 0.80. Healthy participants (18 to 35 years), who were fluent in English, were recruited via an online recruitment system of Leiden University (Sona Systems, Tallinn, Estonia) and via flyers posted in and around the university. Exclusion criteria were as follows: severe physical morbidity (e.g., multiple sclerosis, heart or lung disease), a psychiatric disorder (e.g., clinical depression), chronic pain (≥ 6 months), chronic itch (≥ 6 weeks), pregnancy, and lactation. Participants were instructed to refrain from using painkillers or other medication, alcohol, or any other form of drugs in the 24 hours prior to the test session. If impossible, the appointment was rescheduled or canceled. The study was conducted at Leiden University, Leiden, the Netherlands. The protocol was approved by the Psychology Research Ethics Committee of Leiden University (CEP18-1218/491). The study was pre-registered at the Netherlands Trial Register (NL8072; the relevant registered information can be found via the following link: https://www.trialregister.nl/trial/8072).

Overall procedure

The study used a within-subject design comparing participants' responses to conditioned and control trials in two independent groups (placebo and nocebo group). Participants were stratified for gender for each group. Randomization lists of groups (placebo or nocebo), and first test phase trial type (conditioned trial or control trial) on either dominant forearm or non-dominant forearm were generated before testing commenced by an independent researcher using an online random number generator (www.randomization.com).

Before the experiment, all participants were informed in the advertisement and information letter, as a cover story, that the aim of the study was to investigate the effects of a new device, called an "Electrical Nerve Stimulator (ENS)", on pain and itch. This device was used to serve as a placebo treatment in the study. Once in the lab, all participants gave written informed consent after being provided with an oral explanation of the procedure. Subsequently, they filled out an online screening questionnaire via Qualtrics (Provo, UT, USA) to check eligibility for participation. Eligible participants filled out additional psychological questionnaires.

Once individual intensities for the heat and pressure pain stimuli had been calibrated, the main study began (see Figure 1 for an overview of the design). It comprised three parts. In Part 1, participants either received a positive expectation induction (placebo group) or a negative expectation induction (nocebo group) regarding painful heat stimuli. Participants were not aware of this assignment to the interventions, and the group-allocation was concealed for the experimenters in sequentially numbered, sealed envelopes until the information was required for the procedure. In the first part, the magnitudes of placebo and nocebo effects on heat pain were both learned and tested. In Part 2, generalization of placebo and nocebo effects to pressure pain was tested. In Part 3, generalization of placebo and nocebo effects to cowhage-induced itch was tested. At the onset of Parts 2 and 3, a brief repetition of the heat pain association learned in Part 1 ('reinstatement') was applied, but no expectation induction procedure regarding the pressure pain and the itch stimuli was included. There was around a 4-minute break between each part. During the breaks, participants were free to read magazines with neutral content and to drink water. There was no break between the learning (or reinstatement) and test phase of each part.

At the end of the study, participants filled in a post-assessment questionnaire, were debriefed, and were reimbursed with either study credits or cash. The whole experiment took around two and a half hours and was carried out by two of in total four trained female experimenters following a standard protocol.

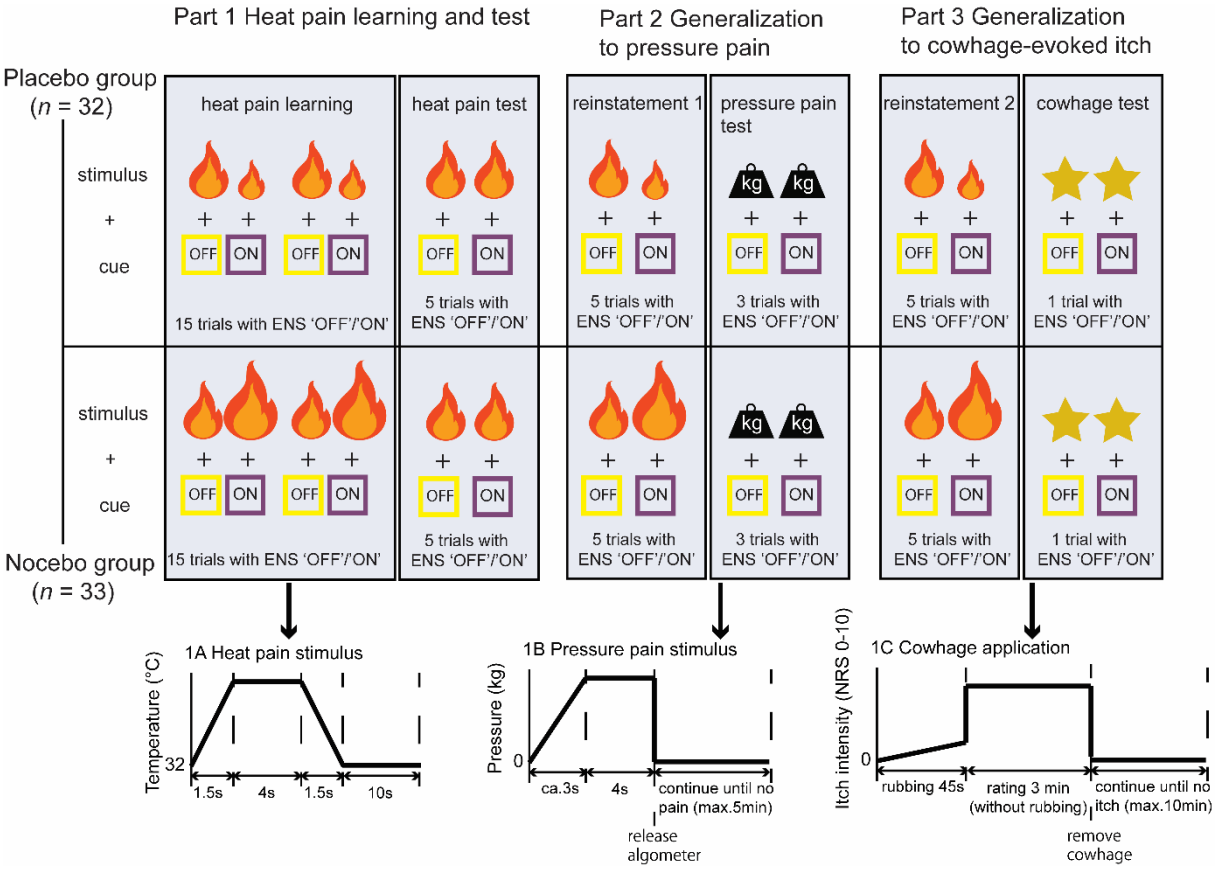

Figure 1. Overview of the main study design. Participants were randomly allocated to 1 of 2 groups: placebo group and nocebo group. A small/moderate/large size picture with red flame represents a low/moderate/high heat pain stimulus, respectively. A picture with "kg" represents a moderate pressure pain stimulus. A gray star represents cowhage spicules. "ENS" was an actual transcutaneous electrical nerve stimulation (TENS) device (model EM80, Beurer, Germany) and functioned as a placebo treatment. "ON" represents a conditioned cue and "OFF" represents a control cue. In order to reduce habituation to heat pain, the thermode was moved once (halfway through the heat pain learning phase) to the corresponding site on the other arm. (1A) timeline of the duration of each heat pain stimulus. (1B) timeline of the duration of each pressure pain stimulus. (1C) timeline of the duration of each cowhage application. ˚C, temperature used in degrees Celsius. kg, kilogram. NRS, numeric rating scale ranging from 0 (no itch at all) to 10 (worst itch imaginable).

Part 1 Heat Pain Conditioning and Test

Part 1 consisted of two phases: the learning and test phase of heat pain. In the learning phase, placebo or nocebo effects on heat pain were induced by verbal suggestion and conditioning in combination with the sham activation of the ENS device. Before the sham ENS device (see Placebo and Nocebo Device) was attached, all participants, depending on group allocation, were given a 1-page handout (see Appendix 1) that described how ENS affects heat pain sensations. Then the handout was simply reinforced by a verbal suggestion. In the placebo group, the verbal suggestion was: *"You have already read how ENS can decrease the pain from heat. Through these electrodes, the device can send light electrical pulses that can affect nerve conduction. This can decrease the heat pain. During ENS, some people report a tingling sensation in the arm or light numbness, but it is completely safe to use and usually causes no side effects, especially not when used only briefly as we will do today. From previous research, we know that it decreases pain in the majority, about 92%, of the people, so when the ENS is on, you'll probably feel less pain from heat.".* The instructions in the nocebo group were exactly opposite to those in the placebo group, i.e., 'increase' and 'more pain' was used instead of 'decrease' and 'less pain'.

Subsequently, heat pain stimuli (see Pain induction) were delivered accompanied by visual cues on a computer screen through E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA), i.e., 'ON' and 'OFF' (in black font) within a purple and yellow colored circle, that indicated the sham (de)activation of the ENS device. Specifically, in the placebo group, conditioning was achieved by surreptitiously using low heat pain stimuli when the conditioning cue ('ON') was shown, and moderate heat pain stimuli during the control cue ('OFF') so that participants would associate the activation of the ENS device with reduced pain. In the nocebo group, the only difference was that participants received high heat pain stimuli instead of low heat pain stimuli with the conditioning cue ('ON'). All participants received 30 trials in the same pseudorandom order: 15 conditioning trials with sham activation of the ENS device and 15 control trials without activation of the ENS device. The test phase followed immediately, with 5 conditioned trials ('ON') and 5 control trials ('OFF') in pseudorandom order (to avoid participants becoming aware of the transition between acquisition and test phase). During the test phase, only moderate heat pain stimuli were applied. One experimenter applied the thermode, while the other experimenter filled in the ratings.

Part 2 Generalization to Pressure Pain

In Part 2, generalization from heat pain to pressure pain was tested. To refresh the association between the heat pain and the ENS device, Part 2 started with a brief repetition of the heat pain learning phase applied during Part 1 ('reinstatement 1'; see Figure 1). The brief repetition was a short version of the heat pain learning phase, and it consisted of 5 conditioning trials with sham activation of the ENS and 5 control trials without activation of the ENS. Subsequently, participants were told that the effects of ENS on pressure pain would be tested. All participants received 6 trials of individually calibrated moderate pressure stimuli (see Pain induction): 3 trials with sham activation of the ENS and 3 trials without activation of the ENS, in a pseudorandom order. Note that 6 pressure pain stimuli, which is less than the 10 heat pain test stimuli, were used for methodological reasons (e.g., sensitization and available space on the hand). One experimenter, unaware of which cues were given, applied the pressure stimuli, while the other experimenter filled in the ratings.

Part 3 Generalization to Cowhage-evoked Itch

In Part 3, generalization from heat pain to itch was tested. After the same brief repetition of the heat pain learning phase used in Part 2 ('reinstatement 2'; see Figure 1), all participants were told that the effects of ENS on itch would now be tested. The amount of cowhage spicules (see Itch provocation) that was previously found to induce moderate itch[1,32] was applied twice: once with sham activation of the ENS and once without activation of the ENS, in a random order. As with pressure pain, one experimenter, unaware of which cues were given, applied cowhage, while the other experimenter filled in the ratings.

Placebo and Nocebo Device

Two electrocardiogram (ECG) electrodes that were connected to a transcutaneous electrical nerve stimulation (TENS) device (model EM80, Beurer, Germany) were attached on each forearm (Figure 2). Participants underwent a short sham ENS-calibration procedure during which they were told that we were setting up an effective and suitable device activation mode by first increasing and then lowering the stimulation to a level just below their perception threshold.[40] This was to make participants believe in the activation of the ENS device despite them not perceiving any activation during the main study. The device actually was never activated during the main study.

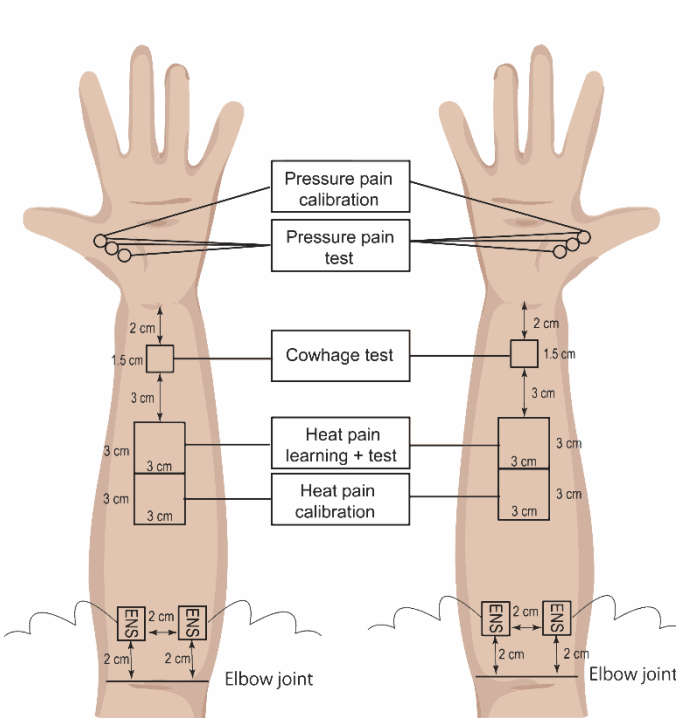

Figure 2. A schematic representation of the volar forearms displaying on which skin areas the pain and itch stimuli were applied as well as the electrodes for the ENS device that functioned as placebo treatment in this experiment. The arm on which the learning and test heat pain stimuli were applied was randomized, and this is an example.

Pain Induction

Heat pain stimuli were delivered to the middle of the forearms (Figure 2) using a TSA-II neurosensory analyzer for sensory testing with a 3 x 3 cm thermode probe (TSA-II; Medoc Advanced Medical Systems, Ramat Yishai, Israel).

Pressure pain stimuli were applied to the subjects' thenar eminence of the hand (Figure 2) using a hand-held algometer (Pain Diagnostic & Treatment, Italy) with a 1 cm diameter probe and a range from 0 to 10 kg.[3]

Throughout the experiment, pain intensities were rated on a numeric rating scale (NRS), from 0 (no pain at all) to 10 (worst pain imaginable). The experienced pain intensities were rated after each heat and pressure pain stimulus in the main study. To assess the effect of expectancies, the expected heat pain intensities were rated before every 5 trials in both learning and test phases in Part 1 and the brief repetition of the heat pain learning phase in Parts 2 and 3. The expected pressure pain intensities were rated before each set of 3 pressure pain stimuli in Part 2. Besides, to assess for any effect of pain on itch, experienced pain intensities were rated at the end of both cowhage-evoked itch trials.

Heat pain calibration and provocations. In order to familiarize with heat pain, participants first received 4 heat stimuli at the self-indicated warmth detection threshold (1 practice trial and 3 calibration trials) and 4 stimuli at the self-indicated pain threshold (1 practice trial and 3 calibration trials). The procedure followed a published standardized protocol.[35] Next, in order

to select the median temperatures that would be used to induce low pain (NRS 0.5 to 2), moderate pain (NRS 3 to 4.5), and high pain (NRS 5.5 to 7), participants underwent two calibration phases. The selected temperatures during these two calibration phases are in accordance with to the NRS ranges described above. In calibration phase 1, participants rated a fixed ascending series of 18 heat pain stimuli in a range from 36°C to 50°C upon which the median of low, moderate, and high temperatures were selected, respectively. In calibration phase 2, participants received a series of maximally 18 heat stimuli that were plus and minus 0.5 °C of the three median temperatures determined in phase 1 in a pseudorandom order. The final three temperatures for low, moderate, and high pain were the median temperatures of all relevant stimuli in calibration phases 1 and 2. For the 2 calibration phases and throughout the main study, all heat stimuli started from a 32°C baseline and increased with a rate of 8°C/s (in ca. 1.5 seconds) until the individually calibrated temperatures for low, moderate, or high pain intensities were achieved, were it was kept for 4 seconds, and subsequently ramped down at 8°C/s rate (in ca. 1.5 seconds).[40]

Pressure pain calibration and provocations. In order to first get familiar with pressure pain, participants received 4 pressure stimuli (1 practice trial and 3 calibration trials) increasing from 0 kg at a rate of ca. 0.5kg/s until participants felt pain for the first time (i.e., the pressure pain threshold). Next, participants received an increasing pressure stimulus during which they were asked to rate pain intensities every ca. 0.5 kg until a moderate pressure pain intensity was reached (NRS pain score between 3 and 4.5). By adding and deducting 0.5 kg of this moderate pressure pain intensity for subsequent stimuli (this procedure was repeated up to a maximum of 4 stimuli), the final consistent median pressure stimulus was selected. For the pressure pain calibration procedure as well as the pressure stimuli in Part 2, all stimuli started from 0 kg with a ramp rate of ca. 1kg/s until the calibrated moderate pressure was achieved, at which it was kept for 4 seconds, and then the pressure was immediately relieved.

Itch Provocation

A number of 40 to 45 cowhage spicules (kindly provided by Dr. Ethan Lerner, Harvard Medical School, Boston, MA, USA) were counted under a microscope (Bresser stereo microscope, Rehden, Germany) using a pair of negative grip tweezers. The spicules were applied within a 1.5 x 1.5 cm^2 area on the volar surface of the forearm near the wrist (Figure 2) by gently rubbing them onto the skin for 45 seconds. Surgical tape (1cm width, 3M, St. Paul, USA) was used to mark the application areas and to prevent spicules from activating the surrounding skin. Participants were instructed to ignore other sensations and to rate only their perceived itch. From the moment at which participants first felt itch, participants verbally reported their itch intensity every 10 seconds for 3 minutes, after which the spicules were carefully removed with surgical tape (3 cm width, 3M, St.Paul, USA).[1,33] After removing the cowhage spicules, participants verbally reported the itch intensity every 20 seconds until they rated 0 (or until a maximum of 10 minutes) and continued to the next cowhage application while presenting the other cue. To assess the effect of expectancies, expected itch intensities were rated before each application of cowhage. Besides, to assess for any effect of itch on pain, experienced itch intensities were rated once at the end of each pain phase (i.e., the heat pain test phase of Part 1, the pressure pain test phase of Part 2, the brief repetition of the heat pain learning phase in Parts 2 and 3). Throughout the experiment, itch intensities were rated on an NRS ranging from 0 (no itch at all) to 10 (worst itch imaginable).

Self-report questionnaires

A screening questionnaire on demographics and health was used to screen participants for exclusion and inclusion criteria. During the screening questionnaire, participants were also asked to rate their levels of fatigue, pain, and itch, on a NRS ranging from 0 (no fatigue/pain/itch at all) to 10 (worst fatigue/pain/itch imaginable). At the end of the experiment, a question assessed the experimenter-participant relationship, i.e., "How trustworthy do you think the experimenters are?" (rated on a 0-10 NRS from "not trustworthy at all" to "most trustworthy imaginable"). Another question assessed the perceived response similarity between pain and itch sensations, i.e., "To what extent do you think pain is similar to itch?" (rated on a 0-10 NRS from "not at all" to "very much"). The perceived purpose of the experiment and participants' belief in the cover story were assessed with open-ended questions, e.g., "What do you think is the purpose of this study?". In addition, several questionnaires were used to assess psychological characteristics, which will be reported in another paper. All questionnaires were administered in English and completed using Qualtrics (Qualtrics, Provo, Utah, United States).

Statistical analyses

All analyses were performed using R (Version 3.6.3, United States) for Windows.[36,39,42,45] Identical data analysis procedures were performed for both the placebo group and the nocebo group (note that these groups were never statistically compared). Missing data were replaced by the last observation carried forward method if possible. The mean and peak pain and itch NRS ratings were calculated. Variables were checked for normal distribution through Shapiro-Wilk tests and inspection of Q-Q plots. The data were screened for univariate outliers using *z*-scores. Univariate outliers were considered *z*-scores above 3.29 or below -3.29. In case of significant deviations from normality, non-parametric Wilcoxon signed-rank tests were performed instead of paired t-tests and were reported in *z* values. Sensitivity analyses without outliers were run on the main outcomes to investigate whether these yielded the same conclusions. All analyses were first run with mean pain/itch ratings across the stimuli for both groups separately, followed by the same analyses with peak pain/itch ratings. For all analyses, the level of significance was set at $P < 0.05$. As effect size measures, Cohen's *d* was calculated for t-tests, with *d* of 0.20 considered as small, 0.50 considered as medium, and 0.80 considered as large; *r* was calculated for Wilcoxon signed-rank tests and was calculated as *z* statistic divided by square root of the sample size (*n*), with *r* of 0.10 considered small, 0.30 considered medium, and 0.50 considered large; generalized eta-squared (η_g^2) was calculated for ANOVA, with η^2 of 0.01 considered small, 0.06 considered medium, and 0.14 considered large.[9,17,28]

Prior to analyses, 1 missing NRS pain score in the heat pain learning phase in the nocebo group, due to human errors, was replaced using the last observation carried forward method. One NRS itch score in the cowhage test phase, 1 expected NRS pain score in the heat pain test phase, 3 expected NRS pain scores in the pressure pain test phase, and 1 expected NRS itch score in the cowhage test phase were missing due to human errors and were not possible to be replaced. As a manipulation check for the induction of placebo or nocebo effects on heat pain, paired samples t-tests were performed by comparing the experienced heat pain NRS ratings during the conditioning/conditioned trials (ENS 'ON') and the control trials (ENS 'OFF'), separately for each phase with heat stimuli (i.e., the learning and test phases of Part 1, as well as the brief repetition of the heat pain learning phase in Parts 2 and 3).

To test the primary outcome of generalization of placebo and nocebo effects from heat pain to pressure pain, the average of the pressure pain NRS ratings during the conditioned trials and the control trials in Part 2 were compared using a paired samples t-test in each group, the

same analyses were used for peak pressure pain ratings. To examine the secondary outcome of generalization to cowhage-evoked itch, the average of the itch ratings during the conditioned trial and the control trial in Part 3 were compared using a paired samples t-test in each group, the same analyses were used for peak itch ratings. Furthermore, we planned to run the same analyses above for heat-pain placebo and nocebo responder separately. Specifically, we defined that heat-pain placebo/nocebo responders have a lower/higher mean pain NRS score for the conditioned trials than for the control trials (> 0) in the placebo/nocebo group, and all other participants were considered non-responders. Additional paired samples t-tests were planned with heat-pain placebo/nocebo responders only to check whether the effects on pressure pain and itch indeed generalized from placebo and nocebo effects on heat pain, respectively. Post hoc, to examine how the effect changes over the time course of the trials, interaction effects between trial type (conditioned/control) and trial number were additionally analyzed using two-way repeated measure analysis of variance (RM-ANOVAs) for all test phases.

As an exploratory outcome, Pearson correlation coefficients were calculated between the expected and experienced responses in the test phases to examine the relation between expectancies and experienced responses, as well as in the learning phase to provide a manipulation check. The expected mean NRS ratings between the conditioning/conditioned trials and the control trials were compared by using a paired samples t-test in each part. The differences in the expected responses between the conditioning/conditioned trials and the control trials as well as the difference in the experienced responses between the conditioning/conditioned trials and the control trials ($NRS_{conditioning/conditioned} - NRS_{control}$) were used. Post hoc, Pearson correlation coefficients were calculated between the induction of the learned placebo and nocebo effects on heat pain and the generalization to pressure pain as well as to cowhage itch in the test phases. In case of significant deviations from normality, Spearman correlation coefficients were performed.

The data will be available via Dataverse (https://dataverse.nl/dataverse/leidenuniversity) upon acceptance of the manuscript.

Results

Participants and temperatures

A total of 97 participants were enrolled in this study. Five participants were unable to complete the study due to the inclusion criteria (e.g., depression), 1 participant quit before filling in questionnaires due to fear of pain, 16 participants were excluded upon the calibration phase due to an inability to stably distinguish the three levels of heat pain intensity during calibration (e.g., the same participant rated one temperature once as moderately painful and another time as highly painful), 6 participants were excluded upon the calibration phase due to exhibiting a too low threshold for pain (i.e., not reaching a low pain rating), 3 participants were excluded upon the calibration phase due to exhibiting a too-high threshold for pain (i.e., not reaching a high pain rating during calibrations), 2 participants were excluded due to technical issues or human errors. In addition, we tested 3 participants fewer than planned due to closure of the labs related to COVID-19. Consequently, a total of 65 participants were included in the final data analysis. In the placebo group, 32 participants (75% female) were included aged 18-33 years (M = 22.0, SD = 3.3). Participants reported low baseline fatigue, pain, and itch levels (M = 3.0, SD = 1.8; M = 0.7, SD = 1.0; M = 0.1, SD = 0.4, respectively). Participants reported a high trust in experimenters (M = 8.7, SD = 1.6), and perceived a low similarity between pain

and itch responses (*M* = 2.4, *SD* = 1.8). In the nocebo group, 33 participants (76% female) were included aged 18-31 years (*M* = 21.6, *SD* = 3.0). Participants reported low baseline fatigue, pain, and itch levels (*M* = 3.2, *SD* = 1.9; *M* = 0.8, *SD* = 1.0; *M* = 0.4, *SD* = 0.9, respectively). Participants reported a high trust in experimenters (*M* = 8.3, *SD* = 2.3), and perceived a low similarity between pain and itch responses (*M* = 2.3, *SD* = 2.0). For each group, descriptive data of the calibrated temperature levels and pressure intensities are listed in Table 1.

Table 1. Group means and standard deviations (SD) for calibrated temperatures and pressure intensities.

		Placebo group (mean (SD))	Nocebo group (mean (SD))
Calibrations	Warmth threshold (°C)	33.8 (0.9)	34.1 (1.3)
	Heat pain threshold (°C)	41.9 (3.2)	41.1 (3.4)
	Low temperature (°C)	42.5 (3.5)	42.2 (3.5)
	Moderate temperature (°C)	46.4 (2.3)	45.6 (2.7)
	High temperature (°C)	48.3 (1.4)	47.8 (1.8)
	Moderate pressure (kg)	4.8 (1.6)	4.7 (1.6)

°C, temperature used in degrees Celsius. kg, kilogram.
Itch induction was not calibrated, but a standard intensity was used for each participant.

Check for pureness for induced sensations

To check whether the stimuli induced pure sensations, itch ratings in the pain phases and pain ratings in the itch phase were assessed. In the placebo and nocebo group, participants experienced significantly lower itch than pain in the pain phases, and significantly lower pain than itch in the cowhage-evoked itch test phase (the descriptive data are reported in Appendix 2).

Manipulation checks for effects on heat pain

As a manipulation check, the magnitude of placebo and nocebo effects on heat pain was analyzed by comparing the heat pain ratings between the conditioning/conditioned trials and the control trials during the learning and test phases of Part 1 and the brief repetition of heat pain learning phase in Parts 2 and 3 (see Table 2).

Learning phase*.* In the placebo group, both mean and peak experienced heat pain were significantly lower during the conditioning trials than the control trials ($t(31) = 20.05$, $P < 0.001$, $d = 3.14$; $t(31) = 16.94$, $P < 0.001$, $d = 2.81$, respectively). In the nocebo group, both mean and peak experienced heat pain were significantly higher during the conditioning trials than the control trials ($z = -5.00$, $P < 0.001$, $r = 0.87$; $t(32) = 7.82$, $P < 0.001$, $d = 1.09$, respectively).

Test phase. In the placebo group, both mean and peak experienced heat pain were significantly lower during the conditioned trials than the control trials ($t(31) = 4.51$, $P < 0.001$, $d = 0.41$; $t(31) = 4.57$, $P < 0.001$, $d = 0.44$, respectively). In the nocebo group, both mean and peak experienced heat pain were significantly higher during the conditioned trials than the control trials ($t(32) = 4.36$, $P < 0.001$, $d = 0.23$; $z = -2.96$, $P = 0.003$, $r = 0.53$). According to our criteria described above, 8 out of 32 participants in the placebo group and 7 out of 33 in the nocebo group were non-responders.

Brief repetition of the heat pain learning phase*.* In the placebo group, both mean and peak experienced heat pain were significantly lower during the conditioning trials than the control trials in the brief repetition of heat pain learning in Part 2 ('reinstatement 1') ($t(31) = 15.59$, $P < 0.001$, $d = 2.61$; $t(31) = 17.85$, $P < 0.001$, $d = 3.16$) and in the brief repetition of heat pain

learning in Part 3 ('reinstatement 2') ($t(31) = 16.92$, $P < 0.001$, $d = 2.76$; $z = -4.94$, $P < 0.001$, $r = 0.88$). In the nocebo group, both mean and peak experienced heat pain were significantly higher during the conditioning trials than the control trials in the brief repetition of heat pain learning in Part 2 ('reinstatement 1') ($t(32) = 11.86$, $P < 0.001$, $d = 2.00$; $z = -4.94$, $P < 0.001$, $r = 0.87$), and in the brief repetition of heat pain learning in Part 3 ('reinstatement 2') ($z = -5.00$, $P < 0.001$, $r = 0.87$; $z = -4.71$, $P < 0.001$, $r = 0.86$).

Table 2. Mean (SD) and peak (SD) NRS ratings for pain and itch evoked during the different pain and itch stimuli applied, reported for the placebo and nocebo group separately.

	placebo group				nocebo group			
	mean rating		peak rating		mean rating		peak rating	
Phase	conditioned	control	conditioned	control	conditioned	control	conditioned	control
heat pain learning	0.9 (0.7)	3.8 (1.1)	2.2 (1.2)	5.6 (1.2)	5.9 (1.1)	3.3 (1.4)	7.2 (1.0)	5.8 (1.5)
heat pain test	2.6 (1.4)	3.2 (1.4)	3.2 (1.5)	3.8 (1.4)	3.3 (1.9)	2.9 (1.8)	4.2 (2.0)	3.8 (2.0)
reinstatement 1	0.7 (0.7)	3.7 (1.4)	1.2 (1.1)	5.0 (1.3)	5.8 (1.3)	3.1 (1.5)	6.7 (1.1)	4.8 (1.7)
reinstatement 2	0.5 (0.6)	3.7 (1.3)	1.0 (0.9)	5.2 (1.2)	5.6 (1.5)	2.9 (1.4)	6.5 (1.2)	4.9 (1.6)
pressure pain test	2.6 (1.3)	3.4 (1.2)	3.2 (1.5)	3.9 (1.3)	4.3 (1.5)	3.8 (1.5)	5.0 (1.5)	4.6 (1.7)
cowhage-evoked itch test	3.2 (2.3)	3.3 (2.6)	4.6 (2.8)	4.9 (3.1)	3.9 (2.3)	3.3 (2.3)	5.6 (2.7)	4.8 (2.8)

SD, standard deviation. NRS, numeric rating scale ranging from 0 (no pain/itch at all) to 10 (worst pain/itch imaginable).

Primary outcome: generalization to pressure pain

The outcome of generalization to pressure pain was defined as the difference in the average experienced pressure pain ratings during the 3 conditioned trials versus the 3 control trials of the pressure pain test phase in each group (Table 2).

In the placebo group, both mean and peak experienced pressure pain were significantly lower during the conditioned trials than the control trials ($t(31) = 4.38$, $P < 0.001$, $d = 0.62$; $z = -2.96$, $P = 0.003$, $r = 0.55$, respectively). In the nocebo group, the mean experienced pressure pain was significantly higher during the conditioned trials than the control trials ($t(32) = 2.20$, $P = 0.035$, $d = 0.33$, respectively), while no significant differences in peak pressure pain were observed ($t(32) = 1.66$, $P = 0.11$, $d = 0.25$, respectively) (Figure 3). When data of only responders were analyzed, similar results were found for both groups, except that a significant difference was also observed in peak pressure pain in the nocebo group ($t(25) = 2.14$, $P = 0.042$, $d = 0.36$).

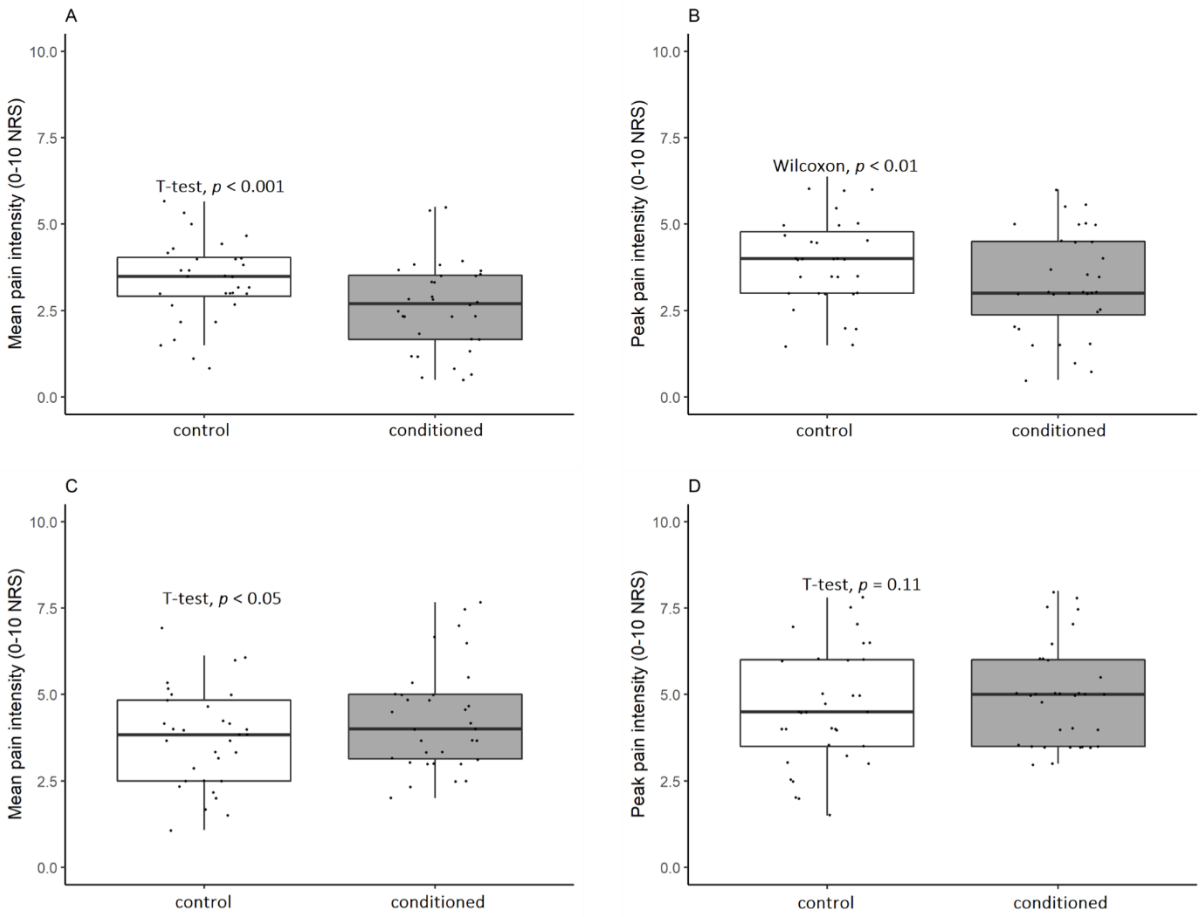

Figure 3. Pressure pain scores compared between the conditioned trials and the control trials, for the placebo and nocebo group separately. Dots represent the (jittered) individual data points. (A) Mean pressure pain scores in the placebo group. (B) Peak pressure pain scores in the placebo group. (C) Mean pressure pain scores in the nocebo group. (D) Peak pressure pain scores in the nocebo group. NRS, numeric rating scale ranging from 0 (no pain at all) to 10 (worst pain imaginable).

Secondary outcome: generalization to cowhage-evoked itch

The outcome of generalization to itch was defined as the difference in itch ratings during the conditioned trial versus the control trial of the cowhage-evoked itch test phase for each group (Table 2).

In the placebo group, there was no statistically significant difference in mean and peak experienced itch in the conditioned trial versus the control trial (z = -0.97, P = 0.33, r = 0.18; z = -0.76, P = 0.45, r = 0.18, respectively). In the nocebo group, there was also no significant difference in mean and peak experienced itch between the different trials (z = -1.44, P = 0.15, r = 0.25; $t(32)$ = 1.43, P = 0.16, d = 0.27, respectively) (Figure 4). For both groups, similar results were found when data of only responders were analyzed.

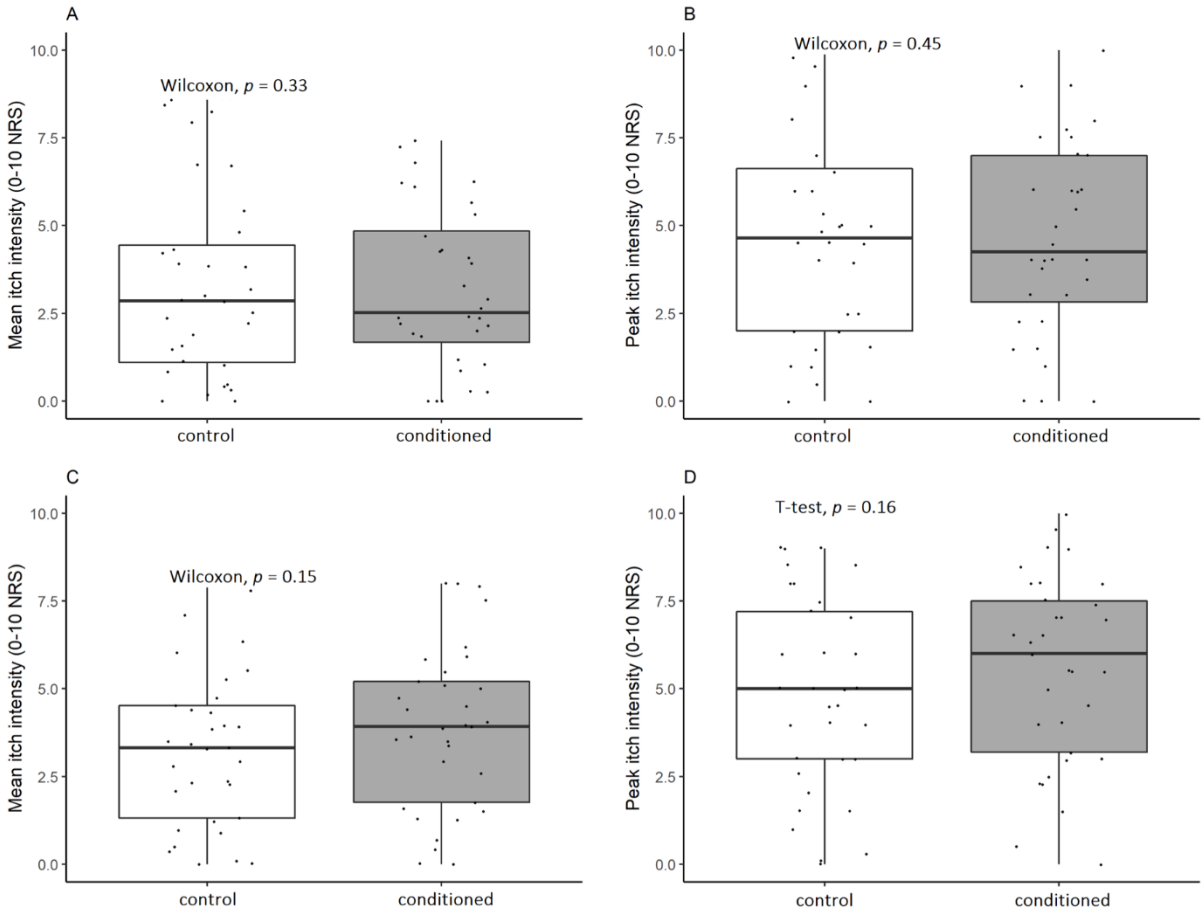

Figure 4. Cowhage-evoked itch scores compared between the conditioned trials and the control trials, for the placebo and nocebo group separately. Dots represent the (jittered) individual data points. (A) Mean itch scores in the placebo group. (B) Peak itch scores in the placebo group. (C) Mean itch scores in the nocebo group. (D) Peak itch scores in the nocebo group. NRS, numeric rating scale ranging from 0 (no itch at all) to 10 (worst itch imaginable).

Relation between expected and experienced responses

The expected pain and itch scores per condition were listed in Table 3. We calculated correlation coefficients between the expected responses and the experienced responses (for both reflected by the difference ($NRS_{conditioning/conditioned} - NRS_{control}$)) of each phase, to further explore the effects of the manipulated expectation on perception of the somatosensory stimuli. In the placebo group, a significant correlation was observed for the association between the mean expected and experienced heat pain in the brief repetition of heat pain learning in Part 3 ('reinstatement 2') ($r = 0.41$, $P = 0.019$), but correlations for other phases were not significant. In the nocebo group, significant correlations were observed for the association between the mean expected and experienced heat pain in the learning phase ($r = 0.50$, $P = 0.003$), in the brief repetition of heat pain learning in Part 2 ('reinstatement 1') ($r = 0.71$, $P < 0.001$), and in the brief repetition of heat pain learning in Part 3 ('reinstatement 2') ($r = 0.68$, $P < 0.001$), but correlations for other phases were not significant.

Table 3. Expected mean (SD) NRS ratings for pain and itch evoked during the different pain and itch stimuli applied, reported for the placebo and nocebo group separately.

	expected rating					
	placebo group			nocebo group		
phase	conditioned	control	*P*	conditioned	control	*P*

heat pain learning	1.9 (1.3)	3.2 (1.2)	***	5.6 (1.2)	3.1 (1.0)	***
heat pain test	1.3 (1.2)	3.8 (1.6)	***	5.5 (1.6)	3.5 (2.0)	***
reinstatement 1	1.3 (1.2)	3.6 (1.4)	***	5.9 (1.3)	3.5 (1.8)	***
reinstatement 2	0.9 (0.9)	4.1 (1.3)	***	5.8 (1.5)	3.8 (1.6)	***
pressure pain test	2.0 (1.2)	3.0 (1.2)	***	4.1 (1.6)	3.3 (1.6)	*
cowhage-evoked itch test	1.8 (1.4)	3.6 (1.7)	***	4.3 (1.7)	3.1 (1.7)	**

"*", 0.01≤p<0.05; "**", 0.001≤p<0.01; "***", p<0.001. P-values were calculated from the comparison of the expected mean NRS ratings between the conditioned and control trials by paired t-tests.
SD, standard deviation. NRS, numeric rating scale ranging from a 0 (no pain/itch at all) to 10 (worst pain/itch imaginable).
The average was taken over 3 trials per condition for the heat pain learning phase and was taken over 1 trial per condition for other phases separately.

Relation between induction of placebo/nocebo effects and their generalization

Placebo effects on heat pain were not found to significantly correlate with the placebo effects on pressure pain (r = -0.041, P = 0.82) or cowhage-evoked itch (r = 0.014, P = 0.94). Also, nocebo effects on heat pain were not found to significantly correlate with the nocebo effects on pressure pain (r = 0.077, P = 0.67) or cowhage-evoked itch (r = 0.0042, P = 0.98).

Post hoc: time-course of sensations

To explore the time-course and learning slopes, line graphs were plotted of the pain evoked by the different pain stimulus trials across phases (Figure 5) as well as of the continuously assessed cowhage evoked itch (Figure 6). Post hoc RM-ANOVAs, for the heat pain test phase showed a significant interaction effect between trial type and trial number in the placebo group ($F(4, 124) = 6.28$, $P < 0.001$, $\eta_g^2 = 0.01$), with the profile plots indicating a reduction of placebo effects over time (Figure 5). In the nocebo group, there was no significant interaction between trial type and trial number ($F(3, 78) = 1.39$, $P = 0.26$, $\eta_g^2 = 0.003$). In the pressure pain test phase, no significant interaction effect was found between trial type and trial number, neither in the placebo group ($F(2, 62) = 0.17$, $P = 0.85$, $\eta_g^2 = 0.0004$), nor in the nocebo group ($F(2, 64) = 0.75$, $P = 0.47$, $\eta_g^2 = 0.002$). In the cowhage-evoked itch test phase, there was also no significant interaction between trial type and trial number, neither in the placebo group ($F(4, 123) = 1.73$, $P = 0.15$, $\eta_g^2 = 0.003$), nor in the nocebo group ($F(3, 92) = 1.41$, $P = 0.24$, $\eta_g^2 = 0.004$).

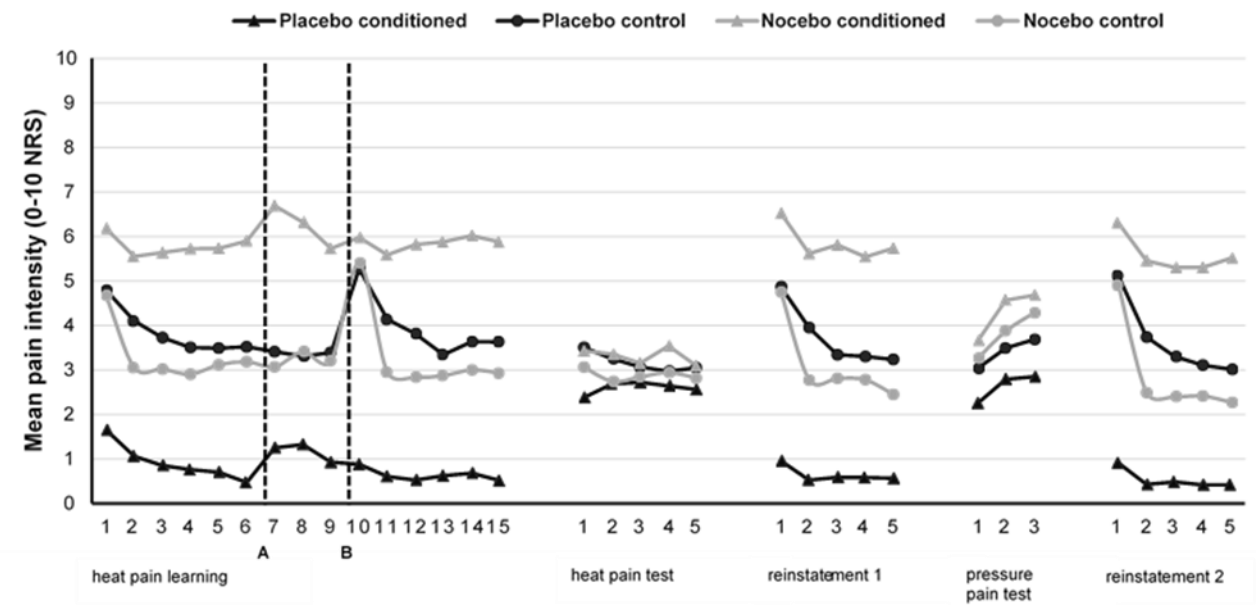

Figure 5. Numeric rating scale (NRS) pain ratings for each trial in the heat pain learning, heat pain test, the two reinstatement, and the pressure pain test phase. The thermode was repositioned halfway the heat pain learning phase: (A) point when the thermode was repositioned during the conditioning trials, (B) point when the thermode was repositioned during the control trials.

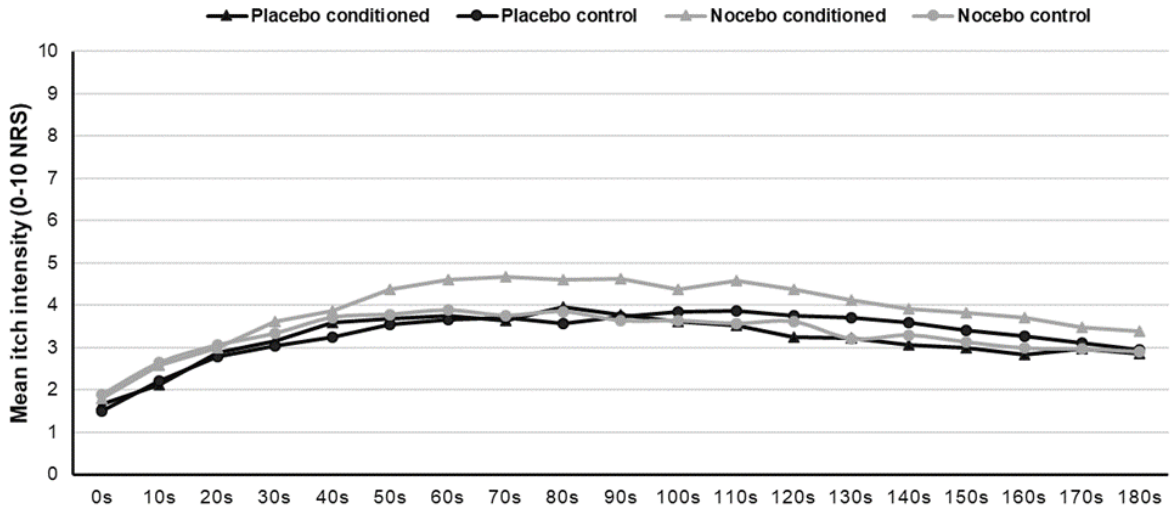

Figure 6. Numeric rating scale (NRS) itch ratings for the conditioned and control trials in the cowhage-evoked itch test phase.

Discussion

The current study shows for the first time that learned placebo and nocebo effects on heat pain, induced by verbal suggestions and classical conditioning, can generalize from heat pain to pressure pain, but not from heat pain to cowhage-evoked itch. Thus, learned placebo and nocebo effects can generalize within pain modalities but may not always generalize across stimulus modalities.

The observed placebo and nocebo effects on heat pain induced by verbal suggestion and conditioning are consistent with several previous studies.[10,34,40] These effects were evident from both mean and peak pain scores that were lower for the placebo conditioned trials and higher for the nocebo conditioned trials as opposed to the control trials during the test phase. In addition, pain and itch evoked in this study were relatively pure; in fact, itch intensities were significantly lower than pain intensities during the pain phases, and vice versa in the itch phase. Establishing placebo and nocebo effects at first as well as inducing divergently pure sensations are prerequisites to study generalization of placebo and nocebo effects within and across sensations.

Our results, in line with our hypothesis, show that the learned placebo and nocebo effects on heat pain affected pressure pain sensations upon presenting the previously conditioned cue, but without presenting verbal suggestion and conditioning directly related to pressure pain. This result is indicative for response generalization of placebo and nocebo effects from pain to another pain stimulus in accordance with an indirect finding of generalization of nocebo effects from electrical itch to histamine-evoked itch.[2] The mechanism underlying response generalization within these pain stimulus modalities may relate to both these signals being associated with myelinated A-delta fiber and mechanosensitive C-fibers when the pressure is painful,[44] although deep pressure pain is mainly conveyed by the myelinated A-beta fibers which differ from those for heat pain and the specific receptors that respond to pressure and heat pain diverge too.[14,20,31] Moreover, although heat and pressure pain are clearly distinct

sensations in everyday and lab experience, participants may perceive and conceptualize these two different pain stimuli simply as “pain” since both stimuli are capable to elicit painful sensations. This is further strengthened by the instruction to rate pain intensity on the same scale for both heat and pressure stimulation. Consequently, people may form the same expectations for pressure pain (Table 3) by recollecting prior experiences of heat pain during the same cue, which consequently affect the sensations.[10,11,23,41]

Placebo and nocebo effects on heat pain were not found to generalize to cowhage-evoked itch as we hypothesized. This contrasts with previous studies demonstrating that placebo effects generalized from pain to fatigue[7] and from pain to negative emotion.[46] Several explanations for not observing generalization from pain to itch can be provided. First, a perception of the (dis)similarity between sensations may affect the likelihood of generalization; people may not expect similar responses to current sensations when they recognize a distinct difference between the current sensations and prior sensations. The distinction between heat pain and cowhage is underlined by the unicity of the peripheral receptors.[8,30] However, these signals are both conveyed by unmyelinated, mechanosensitive C-fibers (C-MSA) and myelinated A-delta fibers.[24,38,45]Needless to say, pain and itch are perceived as more distinct sensations than different types of pain sensations. Participants in our study also indicated to perceive a low similarity between pain and itch responses. Second, although a previous study[4] indicated that nocebo effects on cowhage-evoked itch could be induced by conditioning and verbal suggestions, it might be that cowhage-evoked itch is less prone to be altered by expectations than other types of itch, including histamine and electrical stimulation, that have been repeatedly studied in placebo and nocebo research.[2,5] Third, order effects should be considered as cowhage stimuli were tested after the first generalization effect (i.e., from heat pain to pressure pain). It could be that fatigue might also affect participants’ performance near the end of the experiment, possibly causing them to pay less attention to the (de)activation of the ENS device. Therefore, whether placebo and nocebo effects can generalize from pain to itch remains unclear.

Several limitations of this study have to be taken into account. First, we opted for a solid calibration procedure since we wanted to make sure that each participant could stably distinguish three different pain levels: low, moderate, and high pain. However, the lengthy procedure might have fatigued participants, and consequently affected the results. Moreover, it led to the exclusion of a relatively high number of participants, hence results may not be representative for the entire age group. Despite this limitation, the calibration procedure successfully helped to elicit stable placebo and nocebo effects on heat pain which was required as a first step. In future studies, it would be important to develop a short but effective standard calibration procedure to effectively evoke different pain levels. Another possible limitation of our study is that the colored cues used during the learning and test phase to indicate that the device was ON and OFF were the same over all participants (i.e., the conditioned cue was always a purple circle, and the control cue was always a yellow circle). Possibly, counterbalancing the colors of the cues could have resulted in other findings.

Several implications for future research should be discussed. First, the perception of similarity between sensations could play an important role in facilitating the generalization of the learned effects. Future studies should further explore whether placebo and nocebo effects can generalize between pain and itch perhaps by providing information about the overlap between pain and itch responses. Second, as this study was tested in a single session, it would be interesting to see whether the generalization of placebo and nocebo effects persist, and if so, how it extinguishes. Third, although present findings do not indicate that people who have

higher induced placebo or nocebo effects have larger generalization effects, it remains to be investigated whether placebo and nocebo responders are more prone to generalization effects. Future studies should address whether and how certain individual characteristics play a role in generalization of placebo and nocebo responses. Finally, previous experimental studies demonstrate that emotions, such as fear and anxiety, are especially important to disclose the mechanisms underlying placebo effects, nocebo effects, and generalization.[15,22] For example, investigating whether and how fear or anxiety sensitizes the process of generalization of placebo and nocebo effects within and across stimulus modalities, would provide a better understanding of the underlying mechanisms.

For clinical practice, our main findings probably imply that previous experiences of the course of symptoms or treatment outcomes could partly predict the outcomes for similar symptoms or situations. When considering the ease of generalization of nocebo effects within a stimulus modality, the encounter of repetitive failure of treatments in patients might partly be caused by generalization of negative experiences with treatments to similar situations.[13,47] On the other hand, as placebo and nocebo effects on pain do not seem to transfer to itch, it could be speculated that prior treatment successes or failures for one symptom may not affect the current treatment outcomes on symptoms viewed as distinct from the previous. Thus, in clinical practice, strengthening the distinction in symptoms as well as their treatments' environments may help in reducing the impact of negative treatment history. Future research should focus on how to attenuate the negative association to minimize the generalization of nocebo effects and in the long-run to break a repeated-failed-treatments cycle. Gaining a better understanding of what causes the generalization of placebo and nocebo effects, like verbal instructions and prior experience, on related treatment outcomes, could eventually help improve treatment success. Future studies also could investigate how a comparable short refreshing of learned associations (akin our reinstatement procedures) could be applied in clinical contexts. For instance, health care providers could remind a patient of positive previous experiences with treatments for similar complaints in the past, to improve treatment outcomes.

To summarize, placebo and nocebo effects were, for the first time, found to generalize within pain modalities via the presentation of the same cues. However, there was no evidence for the generalization of placebo and nocebo effects from pain to itch. Future studies into the mechanisms and boundaries of response generalization, including how to strengthen generalization of placebo effects and minimize generalization of nocebo effects, could in the long-term contribute to improvement of pain and itch treatments.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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