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RESEARCH ARTICLE

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Induction and generalization of nocebo effects on itch

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Abstract

Nocebo effects, that is, negative treatment outcomes due to negative expectancies, can increase itch. Moreover, indirect evidence has shown that nocebo hyperknesis can generalize to another itch modality. Knowledge on response generalization can help to prevent and decrease negative effects. The aims of this study were to investigate (1) the efficacy of inducing nocebo effects on cowhage-evoked itch via verbal suggestions and (2) whether these effects can generalize to (2a) mechanically evoked touch and (2b) mechanically evoked itch. Forty-four healthy participants watched a video suggesting that a nocebo solution increases cowhage-evoked itch and that a control solution does not affect itch. Subsequently, cowhage, mechanical itch, and mechanical touch stimuli were applied. Nocebo effects were measured as the difference in both mean and peak of the outcomes itch and urge to scratch between nocebo and control trials. Main analyses revealed significant nocebo effects on mean and peak itch for all stimuli. For urge to scratch, a significant nocebo effect was only observed for mechanical touch (peak). As mechanical stimuli did not induce pure sensations as planned, posthoc sensitivity analyses were run for mechanical stimuli that individually induced either touch or itch at baseline. These analyses showed similar results for generalization to mechanical itch, but generalization to mechanical touch was non-significant. This study showed that merely verbal suggestion can induce nocebo effects on cowhage-evoked itch and that these effects can generalize to another itch modality. Future studies may examine how to prevent negative experiences from generalizing to subsequent encounters.

KEYWORDS
alloknesis, cowhage, hyperknesis, pruritus, verbal suggestion

1 | INTRODUCTION

Itch and scratching are common symptoms of several dermatologic conditions, such as atopic dermatitis.[1,2] Aggravated itch responses in patients with chronic itch are thought to be related to sensitization processes,[3,4] although meta-analytic evidence is inconclusive.[5] Peripheral and central sensitization can lead to itch evoked by tactile stimuli (called alloknesis) and increased itch provoked by normally pruritic stimuli (called hyperknesis).[6] Alloknesis can also occur in areas surrounding itchy skin. These areas probably are larger for

patients with chronic itch than for healthy individuals, although evidence is mixed.[5] Increased itch may also be explained by the involvement of psychophysiological top-down mechanisms such as expectancy that modify sensation perception.[7] Symptom exacerbations by negative expectancies are known as nocebo effects.[8]

Negative expectancies contributing to nocebo effects can be effectively shaped by verbal suggestions.[9] Through providing explicit information about itch, verbal suggestions can induce or modify expectancies for itch and thereby affect itch[10] (eg by telling that a solution can increase itch before applying the solution). This has been studied using several pruritogens (eg histamine, electrical, and mechanical stimulation).[9,11,12] So far, only one study indicated conditioning can induce nocebo hyperknesis using cowhage spicules (derived from the tropical bean mucuna pruriens).[13] A single spicule can induce non-histaminergic itch for several minutes and notably elicit cutaneous dysesthesia areas where tactile stimuli can evoke an alloknesis.[14] No studies to date have investigated whether merely verbal suggestion can evoke nocebo effects on cowhage-evoked itch, neither did any studies assess nocebo effects on alloknesis areas.

Previously induced nocebo effects on one sensation can affect other sensations evoked by other, similar stimuli.[15,16] This is called response generalization, where a generalization response is alike the previous response (eg nocebo hyperknesis) to a stimulus, upon exposure to a cue (eg nocebo solution).[17] For instance, indirect evidence showed that nocebo effects generalize from electrically evoked itch to histamine-evoked itch.[15,16] Theoretically, generalization effects are stronger when the outcomes are more similar.[18] Therefore, it is likely that negative expectancies regarding itch substances (eg cowhage), can amplify itch provoked by other itch stimuli such as mechanical stimuli (ie leading to hyperknesis) or generalize to tactile sensations evoked by non-pruritic stimuli (ie leading to alloknesis). However, this has not yet been examined empirically. Understanding generalization of nocebo effects on itch can provide insight into how nocebo effects could naturally play a role in patients with chronic itch.

In this study, our aims were to test the hypotheses that (1) verbal suggestion can induce nocebo effects on cowhage-evoked itch (primary objective), and (2) nocebo effects can generalize from cowhage-evoked itch to (2a) mechanically evoked itch and (2b) mechanically evoked touch (secondary objective). Throughout the study, the primary outcome was mean itch, and the secondary outcomes were peak itch, mean and peak urge to scratch. Furthermore, we explored whether nocebo effects can be induced on alloknesis areas surrounding cowhage sites and whether nocebo effects can be induced on the onset and peak latencies of sensations evoked by cowhage. Additionally, we explored the relationships between expected versus experienced sensations, between induction versus generalization of nocebo effects, and between itch versus urge to scratch. To this end, we first induced nocebo effects on cowhage-evoked itch in healthy participants via verbal suggestion and subsequently tested responses to cowhage spicules, mechanical itch, and mechanical touch stimuli.

2 | METHOD

2.1 | Participants

The sample size was calculated based on a related previous study.[15] Power analysis in G-power[19] indicated a required total sample size of 44 participants (effect size $d = 0.5$, power = 0.9, $\alpha = 0.05$). In case of data loss (eg dropout), up to 11 participants (25%) would be replaced. The participants were required to be between 18 and 35 years old and fluent in the English language. Exclusion criteria were severe medical or psychiatric conditions, suffering or having suffered from chronic itch (≥6 weeks), currently using medication or drugs, being pregnant or lactating. Participants were also excluded when experiencing spontaneous itch ≥3 on a 0 (no itch at all) to10 (worst itch imaginable) numerical rating scale (NRS) at the start of the testing session and when insensitive to cowhage (ie rated itch as 0 on 0 [no itch at all] to 10 [worst itch imaginable] visual analogue scale [VAS]). Participants were asked to avoid consuming alcohol or drugs in the 24 h before the experiment. Participants were recruited via online advertisements and flyers. The study was conducted at Leiden University, the Netherlands. The study was approved by the Psychology Research Ethics Committee of Leiden University (CEP 19-1205/571) and was preregistered at the Netherlands Trial Register (NL8808, https://www.trialregister.nl/trial/8808).

2.2 | Design and procedure

The study used a within-subject design comparing participants' responses to nocebo and control trials. An independent researcher randomized the type of the first trial (nocebo trial or control trial), baseline measurement on either the dominant or non-dominant forearm, type of mechanical stimuli started with (mechanical itch or mechanical touch), and the order of the sites for the mechanical stimuli (Figure 2). Participants were stratified for gender. Randomization lists were created by the independent researcher.

2.2.1 | Pre-experiment

All participants were informed in the advertisement and the information letter, as a cover story, that the aim of this study was to investigate the psychological and physiological reactions to an active compound “cyclosol” that increases cowhage-evoked itch.

2.2.2 | Preparations and baseline assessments

One of 5 trained experimenters conducted the experimental procedure. Upon arrival at the laboratory, participants were provided with an oral explanation of the procedure and gave written informed consent. Then, participants completed an online screening

questionnaire to check eligibility criteria on Qualtrics (Qualtrics). If participants were eligible, the experimenter opened a sealed envelope containing a randomization list. Participants then did three baseline measurements of (1) mechanical itch sensations, (2) mechanical touch sensations, (3) cowhage-evoked itch sensations (Figure 1). If participants reported no itch to the baseline cowhage measurement within 3 min, cowhage was applied a second time to a corresponding spot on the other arm. If participants did not report

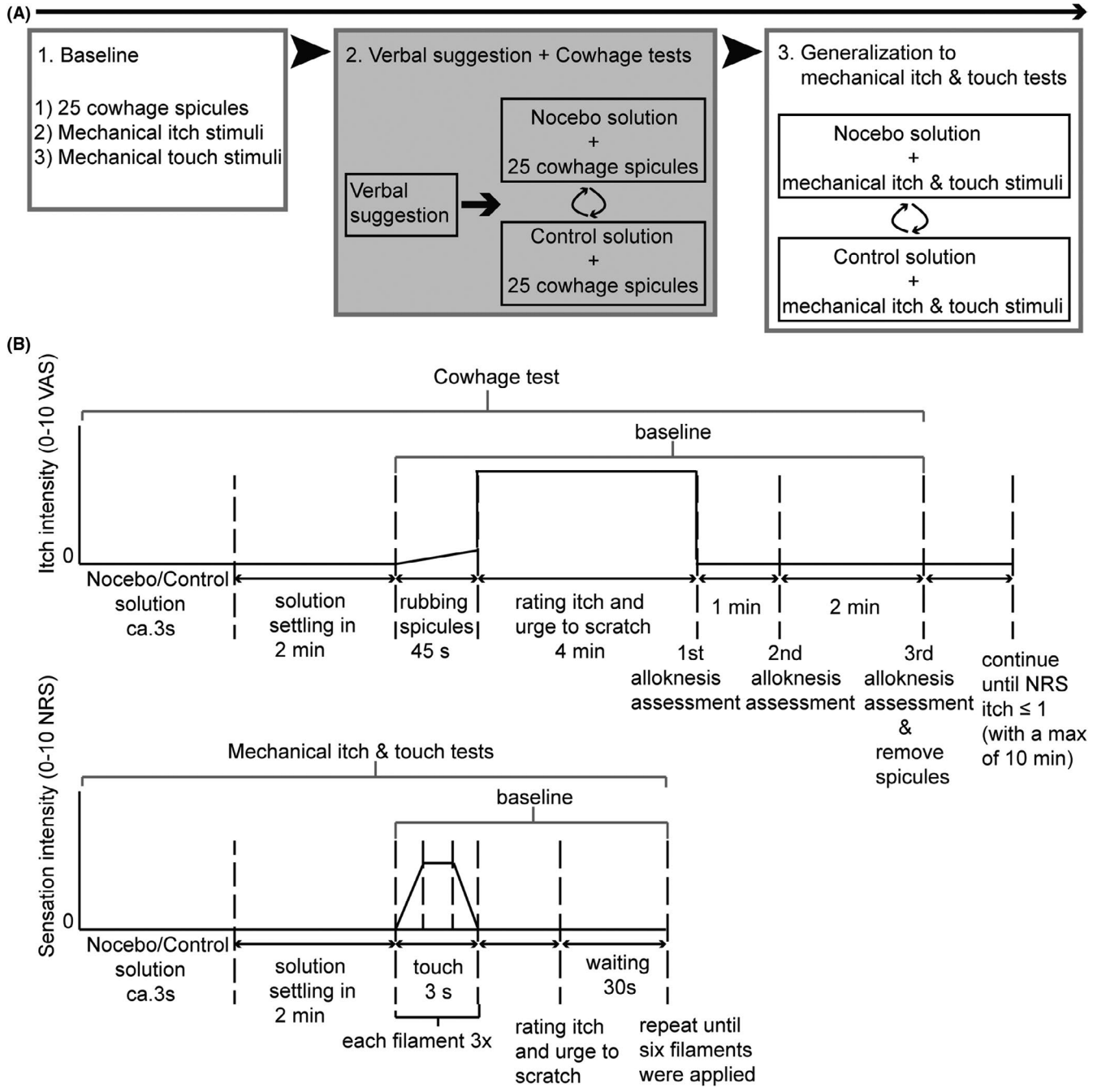

FIGURE 1 Overview of the main design. Panel (A) provides a brief overview of the main study procedure. After baseline assessments of cowhage, mechanical itch, and mechanical touch stimuli, participants received a verbal suggestion that the "cyclosol" solution (nocebo solution) will increase cowhage-evoked itch and the control solution will not affect itch. To assess nocebo effects, either the nocebo or control solution was applied to the application site in randomized order before applying cowhage spicules. Next, to assess generalization, the solutions were applied again before applying mechanical itch and touch filaments. Panel (B) depicts a timeline of the duration of cowhage and mechanical stimuli during the baseline, the nocebo and control trials. Around 25 cowhage spicules were used to induce itch. The filaments that the experimenters preselected for mechanical itch were 4.08, 4.17, and 4.31 mN, and for mechanical touch: 5.07, 5.18, and 5.46 mN. Each filament touched the participant's skin for ca. 3 s, that is, by touching the skin perpendicularly for 1-s until the filament bent, followed by a ca. 1-s keeping on the skin, and another ca. 1-s for gently leaving the skin. These six filaments were applied one after another after applying each solution

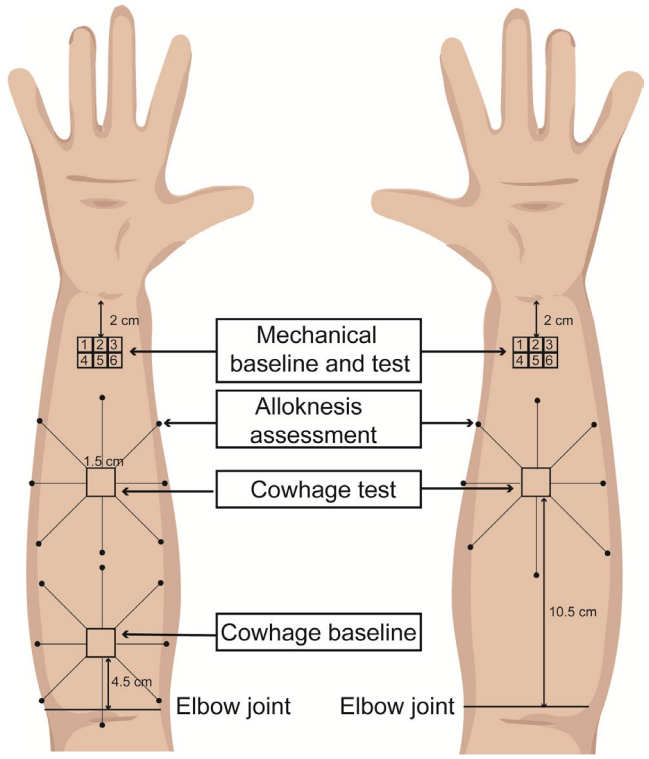

FIGURE 2 Schematic representation of the investigated stimulations on the volar forearms. This is an example of the locations of the cowhage (in the bigger squares), mechanical itch and mechanical touch filaments (both in the smaller squares) for one participant. For each participant, the baseline of cowhage and mechanical stimuli (without cyclosol or control solution) were randomly applied to either the right or left arm. The first solution (either the cyclosol or the control solution) was applied to a different arm from the baseline followed by the first application of cowhage, and the second solution continued with the other arm (ie the same as the baseline arm) followed by the second application of cowhage. Then, this same procedure for mechanical stimuli followed. Cowhage spicules were applied within 1.5 × 1.5 cm area, and filaments were applied within a 2 × 3 cm area (each filament was applied within a 1 × 1 cm area). The filaments for mechanical itch and mechanical touch were randomly applied to one of the sets of sites marked 1, 2, 3, or 4, 5, 6 near the wrist. The brush for alloknesis areas started from 8 black dots surrounding the cowhage applications and moved towards the cowhage application. Note: these starting dots were marked on the skin beforehand

any itch, either they were excluded and reimbursed for their time invested. Otherwise, the main procedure followed with first several psychological questionnaires.

2.2.3 | Main procedure

Participants received a nocebo suggestion that "cyclosol" can increase cowhage-evoked itch (see Nocebo manipulation). Following this, they received cowhage twice, once after application of a solution supposedly containing "cyclosol" (nocebo solution) and once after application of a solution without "cyclosol" (control solution). After each application of cowhage, a standardized sensory brush was used to assess alloknesis areas surrounding cowhage application sites (see Cowhage application and alloknesis assessment).[6] Next, participants received all six filaments for mechanical itch and mechanical touch twice (see Mechanical stimulation), once after the nocebo solution and once after the control solution (Figure 1), without giving any verbal suggestion related to mechanical stimuli.

2.2.4 | Post-experiment

Participants completed a postquestionnaire and were debriefed. The experiment lasted around 1.5 h. Participants received either €11 or course credits for their participation.

2.3 | Manipulation and materials

2.3.1 | Nocebo manipulation

The compound "cyclosol" served as the nocebo treatment. Both the nocebo and the control solutions were simply water. As part of the nocebo suggestion, participants watched a composed video on a desktop computer that described how and why "cyclosol" increases cowhage-evoked itch (Appendix S1). Then, the experimenter orally gave brief instructions that the "cyclosol" solution would worsen cowhage-evoked itch and that the control solution would not affect itch. To make this nocebo treatment credible, one drop of either nocebo or control solution was applied on stimuli application sites and was rubbed in by a Q-tip.

2.3.2 | Cowhage application and alloknesis assessment

Around 25 cowhage spicules can induce low to moderate itch.[20] Cowhage spicules were counted by using a Bresser microscope Advance ICD 10×–160×. A surgical tape with 1 cm width (3M Transpore white) was used to mark the application areas (Figure 2). Spicules were gently rubbed onto each application site for 45 s.[14,20,21] Participants then rated their itch and urge to scratch continuously for 4 min. Subsequently, a sensory brush (SENSElab 05-brush; Somedic, Horby) was gently stroked starting at a distance of approximately 6–8 cm from the centre of a cowhage application site in a centripetal direction from eight different directions (Figure 2).[22,23] The brush head is in contact with the skin at an angle of 45° with a rate of ca. 6 cm/s. During applying each brushstroke, participants marked points where they felt itch for the first time using skin markers.[22,23] The brushstroke procedure was performed at 0, 1 and 2 min after the 4-min rating period upon cowhage application, yielding 3 alloknesis areas per trial. The marked points were transferred to transparent sheets. Then, spicules were removed using surgical tape with 3 cm width (3M Transpore white).[20,21] To allow sensations to diminish, a

break was given until ratings were lower than 1 on a 0–10 VAS or otherwise until 10 min passed.

3.2.1 | *Measuring cowhage sensations*

Participants rated itch and urge to scratch on a digital VAS by using an eVAS app (Aalborg University) installed on a tablet (Lenovo TB2-X30F). The itch and urge to scratch VAS ranged from 0 (no itch/urge to scratch at all) to 10 (worst itch/urge to scratch imaginable). The 4-min ratings were sampled at a rate of 0.2 Hz, yielding 49 ratings per trial. Additionally, participants rated the expected levels of itch and urge to scratch after applying each solution, yet before each cowhage application.

3.2.2 | *Alloknesis area calculations*

Two independent raters connected the marked points to determine the border of the alloknesis area surrounding each cowhage application site and calculated the alloknesis areas (cm^2) by using ImageJ software (developed at the National Institute of Health).[14,22]

2.3.3 | Mechanical stimulation

Semmes-Weinstein von Frey filaments (North Coast Medical) were used to induce mechanical touch and itch. Filaments were applied within a 2 × 3 cm area (1 × 1 cm area per filament) on the forearm (Figure 2). Based on previous studies, e.g.,[24,25] the following 3 filaments were selected to evoke mechanical itch: 4.08, 4.17, and 4.31 mN. After some piloting, 3 other filaments (5.07, 5.18, and 5.46 mN) were selected to evoke mechanical touch. Filaments were applied using the same methodology as described in previous studies,[25,26] that is, a filament was applied by touching the skin perpendicularly for 1 s until bent, followed by a ca. 1-second keep, and another ca. 1 s for gently leaving the skin. This was repeated until a filament had touched the skin trice. Participants then rated their itch and urge to scratch. The interval between two different filaments was around 30 s. Six filaments were applied one after another after each solution. There was no break between the trials.

3.3.1 | *Measuring mechanical stimuli sensations*

Participants rated expected and experienced itch and urge to scratch evoked by mechanical stimuli on a digital NRS (with the same anchor points as the VAS used during cowhage) using Qualtrics on a desktop computer. Participants rated the expected levels of itch and urge to scratch after applying each solution, yet before applying the filaments, yielding one expected itch score and one expected urge to scratch score for all six filaments. Participants rated the experienced levels of itch and urge to scratch after each filament. Additionally, participants were asked whether they felt the stimuli ("Did you feel the stimulus?"—yes or no) at the baseline, nocebo and control trials to make sure that a zero rating for the NRS itch was not because the participant was not feeling the stimulus. Also, participants were asked whether they felt pain ("Did the stimulus evoke pain?" - yes or no) at baseline. If they felt pain, participants rated their pain on a digital NRS from 0 (no pain at all) to 10 (worst pain imaginable).

2.4 | Questionnaires

A screening questionnaire on demographics and health was used for exclusion and inclusion criteria. Participants rated their levels of spontaneous pain, fatigue and itch on an NRS ranging from 0 (no pain/fatigue/itch at all) to 10 (worst pain/fatigue/itch imaginable) at baseline before testing started. In addition, several questionnaires were used to assess psychological characteristics, which will be reported on in another paper. A few check questions were checked at the end of the experiment (Appendix S2). All questionnaires were administered in English and completed using Qualtrics on a desktop computer.

2.5 | Statistical analyses

All analyses were performed using R (Version 3.6.3, US) in Rstudio (version 1.3.959) for Windows.[27] Prior to analyses, missing VAS scores were replaced using the last observation carried forward method ($n = 1$, for the first minute of the cowhage application in both trials due to technical issues). The mean and peak itch and urge to scratch scores induced by each stimulus were calculated separately. Univariate outliers were considered *z*-scores above 3.29 or below -3.29. In case of outliers, main analyses were conducted including outliers, and additional sensitivity analyses were conducted without outliers. Normality was assessed by Q-Q plots and by Shapiro-Wilk tests. In case of non-normal distribution, Wilcoxon signed-rank tests (using *z*-values) were conducted instead of paired *t*-tests. Correlations were calculated with the Pearson correlation coefficient (normal distribution) or the Spearman rank correlation coefficient (non-normal distribution).

To examine the primary objective, paired *t*-tests were conducted between the nocebo and the control trial of itch and urge to scratch evoked by cowhage. Furthermore, we planned to identify the nocebo responders. Specifically, we defined that nocebo responders have a higher mean itch VAS score during the nocebo trial than during the control trial.

To examine the secondary objective, paired *t*-tests were conducted between the nocebo and the control trials of the preselected mechanical itch and mechanical touch stimuli for the itch- and urge to scratch-outcomes. Furthermore, we planned to run the same analyses with cowhage-evoked itch nocebo responders only. Additionally, because we observed that the itch and touch sensations evoked by mechanical stimuli were impure at baseline (ie the mechanical touch filaments evoked itch at baseline and the mechanical itch filaments evoked no itch at baseline), post-hoc sensitivity analyses were conducted. In these sensitivity analyses, we selected per individual, those filaments that evoked either touch or itch at baseline (NRS itch ≤0.1/NRS itch >0.1), and calculated the average of these individualized mechanical touch/itch filaments (labelled as

individualized to distinguish them from the *preselected* filaments) in the nocebo and control trials per participant. Subsequently, we reran the paired *t* tests for these individualized mechanical itch and touch filaments to investigate whether nocebo effects really generalized to mechanical touch and mechanical itch, respectively. NRS itch 0.1 was used as a cut-off for individualized itch or touch sensations due to technical settings (ie participants had to click to confirm rating in Qualtrics, which often results in a score of 0.1 instead of 0).

Several exploratory analyses were run. To explore whether nocebo effects on the alloknesis areas surrounding the cowhage application sites were induced, an intraclass correlation coefficient (ICC) was calculated to assess the inter-rater reliability for two independent raters. If ICC was higher than 0.75,[28] a 2 × 3 repeated measures analysis of variance (ANOVA) was conducted with trial type (nocebo trial/control trial) and timepoint (0 min/1 min/2 min) as within-subject factors with using the ratings of one of the raters. Additionally, the onset latency (defined as the time between the first rating and the first non-zero rating) and the peak latency (defined as the time between the first rating and the peak rating) upon cowhage application were compared between trials using paired sample *t* tests. For each stimulus, average expected itch and average expected urge to scratch were separately compared between trials using paired sample *t* tests. Furthermore, Pearson correlation coefficients were calculated between the expected versus experienced sensations and between the itch versus urge to scratch ratings across all stimuli as well as, between the magnitude of the induced nocebo effects on cowhage versus their generalization to mechanical stimuli.

For all analyses, the level of significance was set at $p < 0.05$ and tests were two-sided. All values are arithmetic means ± standard deviations (SD) unless stated otherwise. As effect size measures, Cohen's *d* was calculated for *t* tests; *r* was calculated for Wilcoxon signed-rank tests; and generalized eta-squared (η_g^2) was calculated for ANOVAs.[29–31]

3 | RESULTS

3.1 | Participants

Of the 46 participants, 2 were excluded (1 due to cowhage insensitivity at baseline and 1 due to a technical problem during the video). Consequently, 44 participants were included in the final data analyses (33 females and 11 males). The descriptive data of each stimulus at baseline are reported in Table 1. Participants' demographics, spontaneous fatigue/pain/itch levels, frequencies of perceiving mechanical stimuli at baseline, and the check questions at the end of the experiment are reported in Tables S1 and S2 and Appendix S2.

3.2 | Primary analyses: Induction of nocebo effects on cowhage-evoked itch

As hypothesized, paired *t* tests showed that both the mean and peak cowhage-evoked itch scores (Table 2, Figure 3) were significantly higher

TABLE 1 Average ± SD for the itch and urge to scratch scores evoked by cowhage and the preselected mechanical stimuli at baseline ($n = 44$)

		Cowhage	Mechanical itch	Mechanical touch
Baseline	Mean itch	1.9 ± 1.4	1.0 ± 0.9	1.0 ± 1.3
	Peak itch	3.3 ± 2.1	1.5 ± 1.1	1.5 ± 1.6
	Mean urge to scratch	1.6 ± 1.5	0.7 ± 0.9	0.8 ± 1.3
	Peak urge to scratch	2.9 ± 2.3	1.1 ± 1.3	1.1 ± 1.6

Note: Participants rated their itch and urge to scratch from 0 (no itch/urge to scratch at all) to 10 (worst itch/urge to scratch imaginable). For cowhage application, 25 spicules were rubbed onto the skin. The preselected filaments for mechanical itch were 4.08, 4.17, and 4.31 mN, and for mechanical touch: 5.07, 5.18, and 5.46 mN.

Abbreviation: SD, standard deviation.

TABLE 2 Average ± SD for the itch and urge to scratch scores during the nocebo and control trials used for assessing nocebo effects on cowhage-evoked itch and their generalization to the preselected mechanical itch and touch filaments ($n = 44$)

	Cowhage		Mechanical itch		Mechanical touch	
	Nocebo	Control	Nocebo	Control	Nocebo	Control
Mean itch	2.2 ± 2.1	1.4 ± 1.5	1.4 ± 1.4	1.1 ± 1.0	1.9 ± 1.8	1.5 ± 1.5
Peak itch	3.5 ± 2.8	2.3 ± 2.2	2.0 ± 1.6	1.6 ± 1.3	2.5 ± 2.0	1.9 ± 1.7
Mean urge to scratch	1.8 ± 2.1	1.2 ± 1.6	1.1 ± 1.4	0.8 ± 0.8	1.4 ± 1.7	1.0 ± 1.4
Peak urge to scratch	3.1 ± 3.0	2.1 ± 2.4	1.6 ± 1.7	1.2 ± 1.2	1.8 ± 1.9	1.3 ± 1.5

Note: Itch and urge to scratch scores were reported from 0 (no itch/urge to scratch at all) to 10 (worst itch/urge to scratch imaginable). For cowhage a application, 25 spicules were rubbed onto the skin. The preselected filaments for mechanical itch were 4.08, 4.17, and 4.31 mN, and for mechanical touch 5.07, 5.18, and 5.46 mN.

Abbreviation: SD, standard deviation.

during the nocebo trial than during the control trial ($t(43) = 2.16$, $p = 0.036$, $d = 0.43$; $t(43) = 2.30$, $p = 0.026$, $d = 0.45$, respectively). Neither the mean nor peak urge to scratch scores were significantly different between trials ($t(43) = 1.56$, $p = 0.125$, $d = 0.31$; $t(43) = 1.88$, $p = 0.068$, $d = 0.36$, respectively). Twenty-eight out of 44 participants were responders (notably, 16 participants showed an opposite response). Figure S1 displays the time-course of cowhage by trial type for all participants.

3.3 | Secondary analyses: generalization of nocebo effects to mechanical stimuli

3.3.1 | Generalization to mechanical itch

The mean and peak itch scores for the preselected filaments to evoke mechanical itch (Table 2, Figure 4) were significantly higher in the nocebo trials than in the control trials ($z = -1.99$, $p = 0.047$, $r = 0.30$; $z = -2.10$, $p = 0.036$, $r = 0.32$, respectively). Neither the mean nor peak urge to scratch scores were significantly different between trials ($z = -1.48$, $p = 0.138$, $r = 0.18$; $z = -1.04$, $p = 0.297$, $r = 0.13$, respectively). Similar results were found in the nocebo responders. Frequencies and the ratings by trial type and preselected filament are reported in Table S2 and Figure S2.

3.3.2 | Generalization to mechanical touch

The mean and peak itch scores for the preselected filaments to evoke mechanical touch (Table 2, Figure 4) were significantly higher in the nocebo trials than in the control trials ($z = -2.33$, $p = 0.020$, $r = 0.36$; $z = -2.25$, $p = 0.025$, $r = 0.33$, respectively). The peak urge to scratch score was significantly higher in the nocebo trials than in the control trials ($z = -2.39$, $p = 0.017$, $r = 0.36$), while no significant difference was reported for the mean urge to scratch score ($z = -1.84$, $p = 0.064$, $r = 0.27$). Similar results were found in the

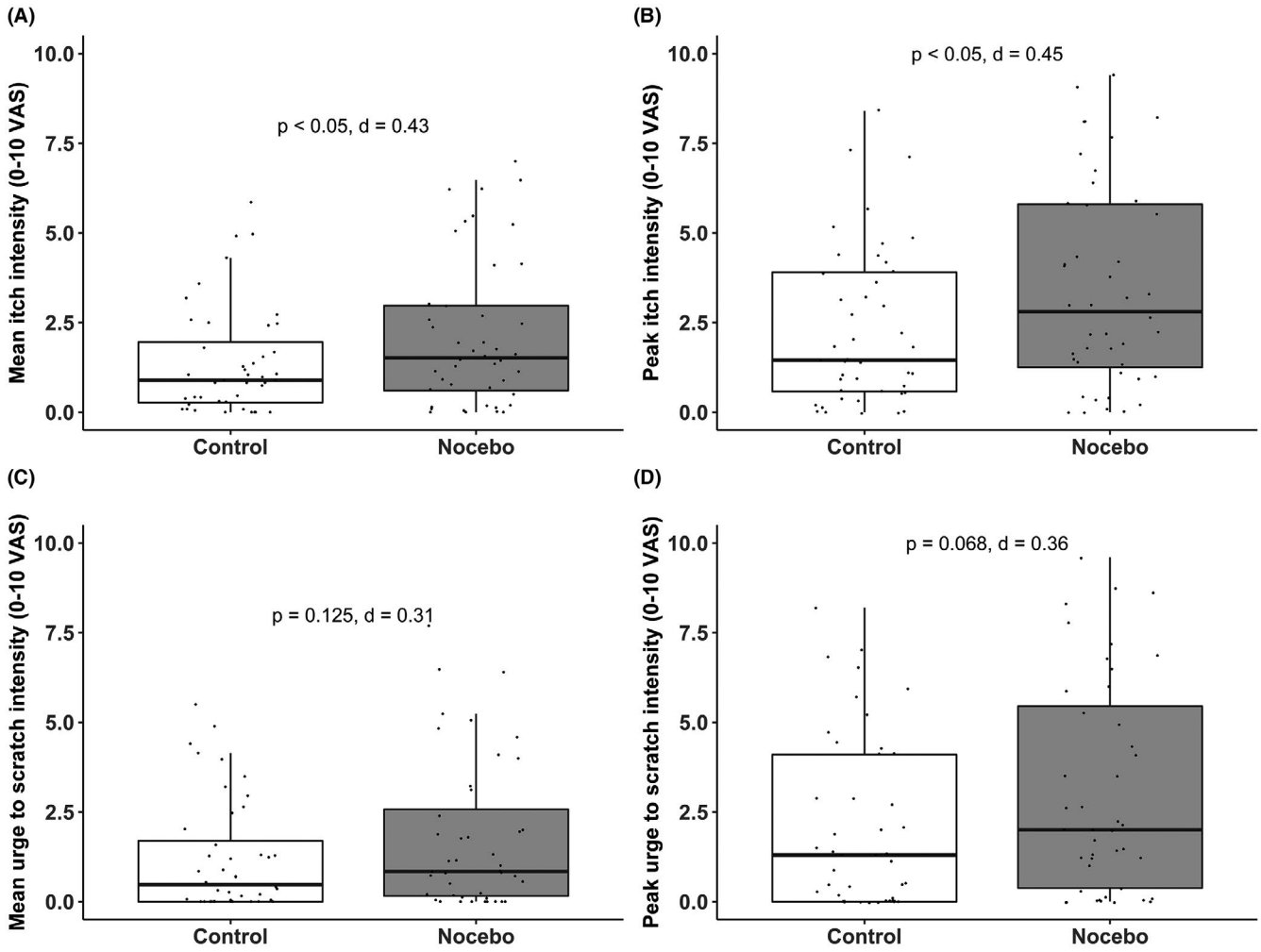

FIGURE 3 Itch and urge to scratch scores compared between the nocebo trial and the control trial for cowhage. (A) Mean itch scores. (B) Peak itch scores. (C) Mean urge to scratch scores. (D) Peak urge to scratch scores. Dots represent the (jittered) individual data points regardless of trial type. VAS, Visual Analogue Scale from 0 (no itch/urge to scratch at all) to 10 (worst itch/urge to scratch imaginable). The boxplots display median ± interquartile range

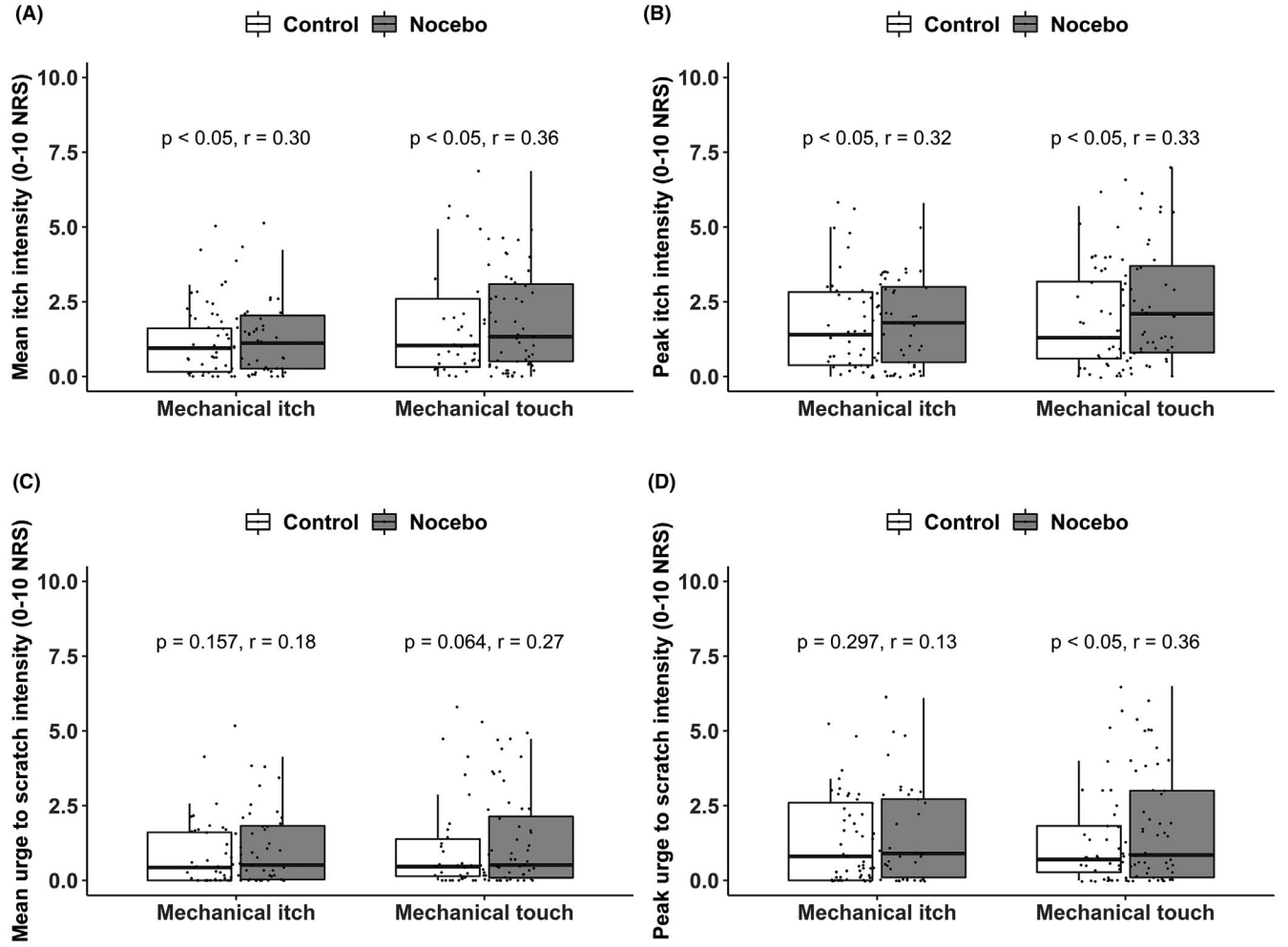

FIGURE 4 Itch and urge to scratch scores compared between the nocebo trial and the control trial for the preselected filaments for mechanical itch (ie 4.08, 4.17, and 4.31 mN) and mechanical touch (ie 5.07, 5.18, and 5.46 mN). Dots represent the (jittered) individual data points regardless of trial type. (A) Mean itch scores. (B) Peak itch scores. (C) Mean urge to scratch scores. (D) Peak urge to scratch scores. NRS, numerical rating scale from 0 (no itch/urge to scratch at all) to 10 (worst itch/urge to scratch imaginable). The boxplots display median ± interquartile range

nocebo responders, except that there was also a significant difference in the mean urge to scratch ($z = -2.49$, $p = 0.013$, $r = 0.45$). Frequencies and the ratings by trial type and preselected filament are reported in Table S2 and Figure S2.

3.3.3 | Sensitivity check

Thirty-nine out of 44 participants rated at least 1 filament as itchy at baseline. Analysing these individualized mechanical itch filaments, the mean and peak itch were significantly higher in the nocebo than in the control trials ($z = -2.71$, $p = 0.007$, $r = 0.44$; $t(38) = 3.15$, $p = 0.003$, $d = 0.29$, respectively). The mean and peak urge to scratch were also significantly higher in the nocebo than in the control trials ($z = -2.13$, $p = 0.03$, $r = 0.34$; $z = -2.11$, $p = 0.035$, $r = 0.35$, respectively). Twenty-nine participants rated at least 1 filament as non-itchy at baseline. Analysing these individualized mechanical touch filaments, no significant difference between trials was reported in mean and peak itch ($t(28) = 1.68$, $p = 0.105$, $d = 0.30$; $t(28) = 1.89$, $p = 0.070$, $d = 0.38$, respectively), nor in mean and peak urge to scratch ($z = -1.93$, $p = 0.053$, $r = 0.34$; $z = -0.56$, $p = 0.57$, $r = 0.065$, respectively). The ratings by trial type and individualized filament are reported in Figure S3.

3.4 | Exploratory analyses

3.4.1 | Alloknesis areas surrounding cowhage application sites

The average intraclass correlation coefficient (ICC) was 0.98 with a 95% confidence interval ranging from 0.97 to 0.99. The 2 × 3 repeated measures ANOVA showed no significant interaction effects between trial type (nocebo/control) and timepoint (0 min/1 min/2 min) of alloknesis areas ($F(2, 86) = 1.29$, $p = 0.28$, $\eta_g^2 = 0.00$). No main effect of trial type was found either ($F(1, 43) = 0.02$, $p = 0.893$, $\eta_g^2 = 0.00$). A significant main effect of timepoint showed that alloknesis areas

decreased over time ($F(1.48, 63.84) = 6.03$, $p = 0.008$, $\eta_g^2 = 0.01$). The descriptive data are reported in Table S3.

3.4.2 | Itch onset and peak latency during cowhage application

Paired *t*-tests showed no differences between the nocebo and control trial in the onset latency of itch and urge to scratch ($t(43) = -0.85$, $p = 0.402$, $d = -0.18$; $t(43) = -1.12$, $p = 0.267$, $d = -0.21$, respectively), nor in the peak latency of itch and urge to scratch evoked by cowhage ($t(43) = 0.47$, $p = 0.640$, $d = 0.10$; $t(43) = -0.11$, $p = 0.914$, $d = -0.02$, respectively).

3.4.3 | Associations between expected and experienced outcomes

The correlations between expected versus experienced sensations were not significant, neither for cowhage (mean itch: $r = 0.21$, $p = 0.182$; peak itch: $r = 0.19$, $p = 0.214$; mean urge to scratch: $r = 0.23$, $p = 0.13$; peak urge to scratch: $r = 0.20$, $p = 0.190$), nor for mechanical stimuli (mean itch: $r_s = 0.06$, $p = 0.688$; peak itch: $r_s = 0.15$, $p = 0.318$; mean urge to scratch: $r_s = 0.08$, $p = 0.607$; peak urge to scratch: $r_s = -0.09$, $p = 0.576$). The descriptive data are reported in Table S4. Note: there was only 1 expected itch and 1 expected urge to scratch rating for the six filaments overall.

3.4.4 | Associations between induction and generalization

Generalization of nocebo effects to mechanical itch filaments was significantly correlated with the induction of cowhage nocebo effects on peak itch ($r_s = 0.40$, $p = 0.007$), but neither on mean itch nor on mean or peak urge to scratch ($r_s = 0.12$, $p = 0.443$; $r_s = 0.14$, $p = 0.381$; $r_s = 0.16$, $p = 0.306$, respectively). Generalization of nocebo effects to mechanical touch filaments was significantly correlated with the induction of cowhage nocebo effects on mean itch ($r_s = 0.30$, $p = 0.048$), but neither on peak itch nor on mean or peak urge to scratch ($r_s = 0.12$. $p = 0.433$; $r_s = 0.23$, $p = 0.140$; $r_s = 0.14$, $p = 0.378$, respectively).

3.4.5 | Associations between itch and urge to scratch

Significant correlations between the itch and urge to scratch ratings were observed. Specifically, higher mean and peak itch were associated with higher mean and peak urge to scratch, respectively, for cowhage stimuli ($r_s = 0.93$, $p < 0.001$; $r_s = 0.92$, $p < 0.001$, respectively), for mechanical itch filaments ($r_s = 0.82$, $p < 0.001$; $r_s = 0.74$, $p < 0.001$, respectively) and for mechanical touch filaments ($r_s = 0.79$, $p < 0.001$; $r_s = 0.69$, $p < 0.001$, respectively).

4 | DISCUSSION

The current study showed, for the first time, that nocebo effects on cowhage-evoked itch can be induced by merely giving verbal suggestions. Moreover, the induced nocebo effects can generalize to mechanically evoked itch, but no convincing evidence showed generalization to mechanically evoked touch. As such, nocebo effects were found to generalize within the itch modality, but generalization from itch to touch remains uncertain.

This study extends previous findings demonstrating that verbal suggestion is sufficient to induce nocebo effects on itch.[9] Through exposing participants to negative information (ie nocebo solution can increase itch), negative expectancies can be triggered to produce nocebo effects and hence exacerbate, in this case, cowhage-evoked itch.[8] This process could probably involve anxiety-related regions (eg amygdala and hippocampus).[8,32,33] Interestingly, exploratory analyses showed that verbal suggestion did not seem to affect the onset latency and peak latency, but only increased the magnitude of itch evoked by cowhage. As such, cowhage, as a non-histaminergic pruritogen, shows to be a promising itch model in future nocebo studies. Moreover, around half of the participants reported alloknesis areas surrounding the cowhage sites, in accordance with previous findings.[6,14] Notably, these alloknesis areas were not affected by verbal suggestion. This finding is in line with previous findings on another physiologic outcome in response to histamine, that is, flare skin reactions (neurogenic).[12] Nevertheless, Stumpf and colleagues demonstrated that nocebo effects on itch can induce larger flare skin reactions.[34] Considering the still limited findings, future research on alloknesis areas surrounding itchy areas can consider using learning processes other than just verbal suggestion (eg classical conditioning). This could lead to understand the process of nocebo effects on alloknesis and further reduce itch dysesthesias.

Our study showed that learned nocebo effects on cowhage-evoked itch can generalize to mechanically evoked itch (nocebo hyperknesis) upon merely applying the same nocebo treatment, yet without direct expectation manipulations, in accordance with the previous indirect and direct indications.[15,16] Several explanations can be provided. First, by receiving the same nocebo treatment, the memory of previous itch experiences could be triggered and elicit the associated negative expectancies.[33,35] Participants thus expected and consequently experienced increased itch evoked by mechanical filaments with the nocebo treatment. Second, having experienced all stimuli at baseline, participants may perceive and conceptualize cowhage and mechanical filaments in the same category (ie as itch-inducing). This is further strengthened by asking participants to rate

sensations on the same itch and urge to scratch scales. Taken together, it is reasonable for nocebo effects to generalize to mechanically evoked itch (nocebo hyperknesis). However, whether learned nocebo effects can generalize to mechanically evoked touch (nocebo alloknesis) remains inconclusive. Although our planned analyses indicated generalization to mechanically evoked touch, sensitivity analyses did not confirm this. Nocebo alloknesis needs to be further investigated to get a better understanding of the severity of negative generalization on itch. Overall, our results support the importance of incorporating psychophysical factors when studying itch dysesthesias—these seem to have been approached mainly from a neurophysiological angle thus far.[6]

Nocebo effects on urge to scratch in the current study yielded mixed results, despite the strong associations between itch and urge to scratch. Previous research did (also) not provide firm behavioural or neurophysiological evidence for nocebo effects on scratching.[34,36–38] This might be because itch stimuli may not be strong enough to induce a stable urge to scratch. Also, verbal suggestions did not pertain to scratching in the current and previous research. Future research can investigate nocebo effects on scratching by manipulating the expectations regarding scratching, while assessing both self-reported scratching and observation of actual scratching behaviours, to aid in further understanding the malleability of scratching behaviour to nocebo effects.

Some implications for future research should be discussed. First, when aiming to investigate generalization of nocebo effects to touch, it is important to use stimuli that induce pure touch sensations; given the large variability in sensitivity across people, more extensive (piloting) research is required to reliably distinguish filaments, or other stimuli, that induce pure touch. Second, as this nocebo itch study consisted of only a single session, further study could investigate how long the induction and (response) generalization of nocebo effects persist. Third, although the findings suggested some links between the induction of nocebo effects and their generalization, it remains unclear whether nocebo responders are more prone to generalization effects than non-responders.[16] Exploring the role of responders' characteristics in generalization of nocebo effects will help in individually predicting the prevalence of nocebo effects. Fourth, it would be relevant to explore associated brain activations (eg expectancies, anxiety, and memory) underlying the process of generalization of nocebo effects. Getting a more comprehensive understanding of the underlying mechanism can be crucial for minimizing nocebo effects in itch treatments.

For clinical practice, our findings of response generalization of nocebo effects probably imply that previous negative treatment experiences could negatively affect outcomes of the same treatment for similar symptoms. Therefore, it may be highly valuable for healthcare providers to be aware of patients' negative treatment history beyond that for the symptom currently under treatment. This further speaks for the importance of preventing negative treatment experiences from occurring. However, this can naturally not always be achieved. Recent research suggests promising interventions for attenuating nocebo effects, such as counterconditioning and positive framing.[15,39,40] Whether such interventions can also prevent generalization of nocebo effects remains to be examined. Studying how to extinguish negative associations in clinical treatments can help minimize generalization of nocebo effects and break a repeated treatment failure cycle. For instance, it is likely that using noticeably different treatments or treatment contexts after an unsuccessful treatment may help in reducing generalization of negative experiences. Previous research indicates that patients with chronic pruritic conditions such as atopic dermatitis are more prone to nocebo-evoked itch than healthy individuals.[5,41,42] Hence, nocebo hyperknesis may be involved in patients' itch reports concerning non-lesional skin, thus maintaining and worsening itch symptoms.[6] Therefore, research in patients is needed to replicate and extend the current findings, to help in increasing the ecological validity of nocebo research and naturally assessing the severity of nocebo effects on itch in clinical settings.

To conclude, this study provides a novel insight into nocebo effects and itch dysesthesias by investigating generalization of nocebo effects within itch modalities and beyond (touch). We found that verbal suggestion can induce nocebo effects on cowhage-evoked itch (nocebo hyperknesis), but not on the alloknesis areas surrounding itchy sites. Nocebo effects were found to generalize from cowhage-evoked itch to mechanically evoked itch (nocebo hyperknesis), while inconclusive evidence was found for generalization to mechanically evoked touch (nocebo alloknesis). Nocebo effects thus can exacerbate pruritic symptoms and even generalize to other pruritic symptoms, which may extend a vicious cycle of itch. Further research into how to prevent and attenuate negative generalization effects on itch could aid in improving pruritic treatments in the long term.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors contributed to designing the study. LW and others mentioned in acknowledgements acquired the data. LW analysed the data. AvL and KP checked the data and R codes. LW drafted the manuscript. LW, AvL, KP and AE critically revised the manuscript. All authors have edited and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this study are available on DataVerseNL (https://doi.org/10.34894/TRRAJI).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

App S1. A composed video (verbal suggestion).

App S2. The check questions at the end of experiment.

Tab S1. Demographics, spontaneous fatigue/pain/itch levels during the experiment of all participants ($n = 44$).

Tab S2. Frequencies of perceiving stimuli, itch and pain evoked by all six filaments during baseline, the nocebo trials and the control trials.

Tab S3. Frequencies and mean of alloknesis areas surrounding cowhage sites during baseline, the nocebo trials and the control trials.

Tab S4. Expected mean ± SD scores for itch and urge to scratch during the nocebo and the control trials of cowhage and mechanical stimuli ($n = 44$).

Fig S1. Visual Analogue Scale (VAS) itch ratings from 0 (no itch at all) to 10 (worst itch imaginable) during the nocebo and control trial in cowhage applications ($n = 44$).

Fig S2. Numeric rating scale (NRS) itch ratings from 0 (no itch at all) to 10 (worst itch imaginable) for the nocebo and control trials of the filaments (numbers depict the force per filament in millinewton (mN)) that were preselected to evoke mechanical itch and touch sensations ($n = 44$ for mechanical itch and mechanical touch). Dots represent the (jittered) individual data points regardless of trial type. The boxplots display median ± interquartile range.

Fig S3. Numeric rating scale (NRS) itch ratings from 0 (no itch at all) to 10 (worst itch imaginable) for the nocebo and control trials in the individualized filaments (numbers depict the force per filament in millinewton [mN]) which were individually selected to induce either itch or no itch at baseline ($n = 39$ for mechanical itch, $n = 29$ for mechanical touch). Dots represent the (jittered) individual data points regardless of trial type. The boxplots display median ± interquartile range.

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