How negative experiences influence the brain in pain: neuroimaging and biobehavioral insights

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Chapter 2.

Learned nocebo effects on cutaneous sensations: Meta-analysis of experimental behavioral findings.

Submitted for publication as

Thomaidou, MA, Blythe JS, Peerdeman KJ, van Laarhoven AIM, Van Schothorst MME, Veldhuijzen DS, Evers AWM. Learned nocebo effects on cutaneous sensations: A systematic review and meta-analysis of experimental behavioral findings.

Abstract

In past decades, the field of nocebo research has focused on studying how sensory perception can be shaped by learning. Behavioral conditioning processes as well as mere verbal suggestions of a negative treatment outcome may aggravate pain and itch perception. Gaining a comprehensive view of the magnitude of nocebo effects and the factors that contribute to their formation will help steer nocebo research towards fruitful directions for better understanding complex sensory phenomena. We conducted a systematic review and meta-analysis of a total of 37 distinct experimental nocebo studies on healthy participants, with four separate meta-analyses for nocebo effects on pain or itch, induced with classical conditioning and verbal suggestion, or verbal suggestion alone. We conducted subgroup analyses and meta-regression on factors such as the type and intensity of sensory stimuli, and the length of learning paradigms. This meta-analysis showed that on average, effect sizes of nocebo effects were moderate to large (Hedges *g* between 0.26-0.71 for the four primary outcomes). The combination of conditioning and verbal suggestions yielded stronger nocebo responses on pain in particular. Subgroup analyses, including factors such as the type of sensory stimulation, did not explain the moderate heterogeneity in nocebo magnitudes between different studies. Risk of bias was generally low and was not related to nocebo magnitudes either. We discuss these results in relation to the role of conditioning as well as aversive learning, and we recommend more consistency in designing and reporting nocebo experiments.

Introduction

Negative expectations regarding the effects of a treatment can result in the aggravation of cutaneous sensations such as pain and itch [1–3]. Such learned responses can be induced experimentally, allowing for the study of processes by which nocebo effects lead to symptom amplification [4–10]. In experimental studies, nocebo responses are defined as a significant increase in a sensation after a nocebo treatment, relative to no-treatment or a control treatment. Negative expectations leading to such responses are typically induced through classical conditioning, verbal suggestions, or their combination [4,5,10–13]. Classical conditioning induces nocebo effects by building implicit associations between an (inert) treatment and the worsening of sensations such as pain or itch [14–16]. Verbal suggestions explicitly provide negative information regarding the pain- or itch-increasing effects of a treatment [7]. Because nocebo studies employ diverse methods, to better understand their potential impact on nocebo outcomes these methodological features warrant a systematic investigation.

Learning has consistently been shown to underlie induced nocebo effects [5–7,9,17], and verbal suggestions seem to induce stronger nocebo responses when combined with conditioning [18]. The positive counterpart to nocebo, placebo effects, also appear to be stronger when induced through a combination of conditioning with verbal suggestions, compared to conditioning alone, both on pain [19] and itch (Bartels et al., 2014; Blythe et al., 2019). One meta-analysis included results from ten nocebo experiments published up to 2013 and reports that the overall magnitude of the nocebo effect was moderate to large and effects were generally larger when verbal suggestions were used in combination with conditioning [18]. That early meta-analysis had a limited sample of studies

available, and an up-to-date review is needed to examine how different types of learning may induce nocebo effects of different magnitudes.

At the same time, other variables, such as the type of sensation (i.e., pain or itch), stimulus modality (e.g., thermal, electrical), the intensity of pain or itch stimulations, and the length of learning in different behavioral paradigms, also require a systematic examination across studies. For example, in experimental nocebo research, some nocebo conditioning paradigms include as few as four associative learning trials (Blythe et al., 2021), while others employ much longer paradigms [6,8,21]. A diverse set of cutaneous sensory induction methods are also used, such as thermal [17], electrical [6,20], or laser pain stimulations [22]. Such methodological choices, often meant to target specific underlying processes in nocebo experiments, can potentially influence nocebo responding and thus merit further investigation.

Given the recent growth of nocebo research, we conducted a systematic review and meta-analysis of experimental nocebo studies in healthy participants to provide novel insights into distinct contributions of methodological factors in the induction of nocebo responses. We focused on cutaneous sensations, aiming to examine nocebo responses induced with comparable sensory inductions externally on the skin. First, we examined nocebo magnitudes between pain and itch and based on the learning method used. Then, we conducted subgroup analyses and meta-regression to assess how the type and intensity of stimulations, the length of learning, the timing of measurement of nocebo magnitudes, and risk of bias in studies may impact nocebo magnitudes.

Methods

Protocol and registration

The protocol for this study was pre-registered on ClinicalTrials.gov (ID: NCT04387851) and conducted based on the PRISMA statement (**Appendix A**) and Cochrane recommendations (2020). The protocol was registered based on a single search strategy for both nocebo and placebo studies, which, due to the volume of the studies returned, is now divided in two separate papers. Here, we report only the nocebo (arms of) experimental studies.

Databases and selection criteria

PubMed, PsycINFO, EMBASE, and the Cochrane CENTRAL Methodology Library were searched to identify studies. Languages were a-priori restricted to English, Dutch, and German and the publication period was not restricted. Searches were initially conducted on March 18th, 2019. Repeated searches for studies published after this time were conducted in June 2020 and July 2021. The detailed key-word strategy for each database will be made available online upon publication (**Appendix B**).

We searched for original, peer-reviewed, controlled experimental studies (or study arms) on healthy human participants that aimed to experimentally induce placebo and/or nocebo effects. Patient samples were not included, to improve the homogeneity of the results, and for the same reason we focused on cutaneous sensations (i.e., pain and/or itch stimulations that were administered on the skin), excluding for

example visceral pain studies. For the purposes of in- and exclusion, studies were considered to have induced a placebo or nocebo effect if a learning paradigm was used to induce positive or negative outcome expectations about an inert treatment. We considered as *nocebo* learning paradigms only those that aimed to induce negative expectations regarding an intervention, such as sham electrical stimulation or an inert cream. This meant that most conditioning without verbal suggestion studies were excluded from this review, as they did not include treatment associations, and were considered to be pain-conditioning, not nocebo-conditioning studies (albeit explicit mention of the terms *nocebo* and *placebo* was not a specific inclusion criterion). Additionally, we only included studies that had a control group or a control condition within-subjects, so that nocebo effects could be calculated as the difference between nocebo and control/no treatment on self-reported scores. We excluded studies that excluded or did not report data from nocebo non-responders. Post-hoc, we excluded observational learning studies as they were too few for a meaningful analysis. Studies that did not fulfill one or more of the criteria mentioned above were excluded from the meta-analysis (see **Figure 1** for a flow diagram).

Study selection

Eligibility assessment for the inclusion of studies was performed independently by two authors in each of the following steps. Titles and abstracts of articles retrieved using the search strategy were screened by two authors independently (M.M.E.v.S. and J.S.B.). The full text of articles to be included and articles about which doubts existed were then retrieved and assessed for eligibility by two authors independently (M.A.T. and J.S.B.). The reference lists of all included articles were also screened for study inclusion by two authors (M.A.T. and J.S.B.) and included articles were also entered in Web of Science to identify articles

that have cited them and should potentially be included in the meta-analysis. When necessary, authors of studies were contacted in order to provide full-text articles that were not accessible online. Any disagreements regarding study inclusion were resolved by consultation with a third author (K.J.P.).

Data extraction

One author (J.S.B.) used a standardized form to independently extract data from the included studies to derive data for analyses. Another author (M.A.T.) checked 25% of extracted values for accuracy. Extracted information included details of the intervention such as the learning method used, the control condition, study population, sensation type, pain/itch rating data, type of cutaneous stimulation (e.g., heat pain, pressure pain), type of outcome expected (i.e., placebo or nocebo), information for quality assessment, and outcome data for meta-analysis (e.g., sample size, pain/itch rating means and standard deviations). Doubts regarding data-extraction were resolved through discussion with a third review author (K.J.P.). Missing data were requested directly from the study authors. When there was no response from authors, but data could be extracted from published figures, this was done using WebPlotDigitizer version 4.4 (Rohatgi, 2020).

Risk of bias

Risk of bias (RoB) was assessed and checked by two authors (M.A.T. and J.S.B.) using the method developed by Marcuzzi and colleagues specifically for quantitative sensory testing studies [23]. This method assesses whether the sample was clearly described and was representative of the population, whether the somatosensory assessment

methods are standardized, validated, and well described, if potential confounders were considered, and adequate blinding. Each category was scored as being satisfied (0 points), not satisfied (2 points), partially satisfied (unclear; 1 point), or not applicable. Scores were selected based on criteria described in Marcuzzi and colleagues [23]. We additionally concocted numerical scores (0-34) for each study, by summing each item score, with higher scores indicating higher risk of bias (please see **Appendix C** for an example of the RoB scoring.

Statistical analyses and results synthesis

All analyses were conducted and checked by two reviewers (J.S.B. and M.A.T), using the Comprehensive Meta-Analysis software (version 3.3.070; Biostat, Englewood, USA) and R programming software for visualizations [24]. Funnel plots were inspected for outliers (i.e., studies falling outside the funnel of expected results), and to assess publication bias across studies we checked for number of imputed missing studies with Duval and Tweedie's trim and fill method [25]. Heterogeneity between studies was assessed with the I^2 statistic and visual inspection of the forest plot. I^2 is a measure of the proportion of observed variance reflecting real differences in effect sizes [26] with values of 25%, 50%, and 75% considered as low, moderate, and high degrees of heterogeneity, respectively [27]. For forests plots, we calculated study weights in *R*, by inversing the variance of each effect size.

Given the heterogeneity of study designs, random effects models were used for all meta-analyses. Effect sizes were calculated using means and standard deviations for each group (between subjects) or trial type (within subjects). [26]. We selected nocebo and control conditions based on what was reported in studies: some reported nocebo magnitudes between groups, other within groups in the first pair of evocation trials,

and others reported nocebo magnitudes as the mean difference of all control and evocation trials. When only nocebo/control difference scores were reported, these were used instead. When only standard errors were reported, they were converted to standard deviations by multiplying the standard error by the square root of the group size (n). For each study, an effect size Hedges's *g*, weighted to the sample size (N), was computed as the mean response in the nocebo condition minus the mean response for control in the evocation phase of experiments. Positive *g* values indicate a nocebo response, with values around .2 considered small, .5 medium, and .8 large.

For studies that used within-subjects comparisons, the nocebo-control condition correlation coefficient could not be derived, therefore an average r of .5 was imputed [28]. Meta-analysis was only conducted when the data of at least 4 studies were available in total. In subset analyses, the effect sizes were compared descriptively rather than with statistical tests when 2 or less studies were available per group. Studies with multiple eligible conditions were treated as separate subgroups and averaged across in CMA (e.g., when cheap vs. expensive inert treatments were used as nocebo, we averaged the results and treated this as one group (see **Table 1** for results synthesis per study).

Primary outcome measures and subgroup analyses

Our primary outcomes were the overall magnitude of nocebo responses (i.e., the difference in self-reported pain/itch between a nocebo and a control trial in the evocation phase) separately for pain and itch studies employing verbal suggestions with or without classical conditioning. We thus computed 4 pooled effect sizes: verbal suggestions in pain, conditioning with verbal suggestions in pain, verbal suggestions in itch, conditioning with verbal suggestions in itch. Whenever possible, the

mean of pain or itch ratings across the entire evocation phase was used. If only values from the first trial(s) were reported, these were used instead, and sensitivity analyses tested for differences in magnitudes between studies reporting the mean versus the first trials.

We also did subgroup analyses to compare Hedge's *g* between nocebo responses based on the type of learning (verbal suggestion or combination with conditioning) and type of sensory stimulation (e.g., thermal, electric) and the timing of nocebo measurement (as the mean of evocation or only the first evocation trials, by trial type). Meta-regression assessed the impact of the length of learning, (quantified as the number of learning trials during induction, while we also separately examined number of trials evocation), the timing of the measurement of nocebo hyperalgesia in the evocation phase (first trials versus mean of evocation trials), the stimulus intensity (calculated as the calibrated difference in pain intensity for control vs. nocebo trials) and the Risk of Bias score on nocebo magnitudes for the included studies.

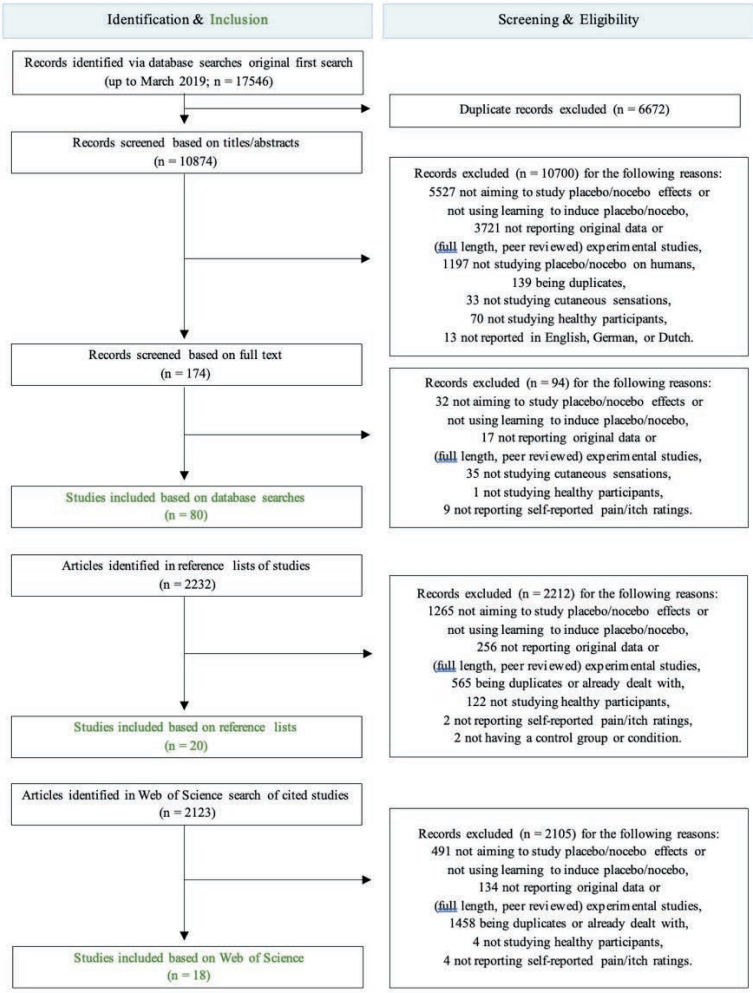
Results

Study selection

Figure 1 shows the flow of the study selection process including the reasons for exclusion at each stage. A total of 17546 nocebo and placebo papers were initially identified through the database searches. We searched for more eligible studies through reviewing the reference lists as well as web of science for each included study, as well as conducting repeat database searches in June 2020 and July 2021. At each stage of

study inclusion, duplicates were removed, and remaining articles were considered based on title and abstract, or full text. In total, we identified 24814 articles through our searches, of which 24687 were excluded.

We did not follow a strict hierarchical approach in marking exclusion criteria, but selected criteria based on what was deemed to be the major exclusion reason, for example when screening abstracts where limited information is available, therefore the following exclusion numbers provide less than precise estimates of exclusion reasons. We excluded articles for the following reasons: 8302 articles for not aiming to study nocebo or placebo effects or not using a learning paradigm to induce placebo or nocebo effects (explicit use of the terms *nocebo* or *placebo* was not an inclusion criterion), 4328 for not reporting original data or (full length, peer reviewed) experimental studies, 1229 studies for not being conducted in humans, 10440 because they were duplicates or already screened during a previous round, 101 articles for not studying (placebo/nocebo on) cutaneous sensations, 242 articles for not studying (placebo/nocebo in) healthy human participants, 20 articles because they did not report self-reported pain/itch intensity ratings, 13 for not being in English, Dutch, or German, 2 studies for not using a within- or between-subjects controlled design, 5 studies for not responding to requests for data, and 5 for excluding data from participants that were considered placebo/nocebo non-responders. A total of 127 articles were selected of which 108 included placebo conditions and 39 nocebo conditions. Of these articles, we excluded 2 observational learning studies as they were too few for a meaningful analysis. Thus, in total, **37** studies were included in this meta-analysis on nocebo effects.


Identification & Inclusion
Screening & Eligibility
Records identified via database searches original first search (up to March 2019; n = 17546)
Duplicate records excluded (n = 6672)
Records screened based on titles/abstracts (n = 10874)
Records excluded (n = 10700) for the following reasons:
5527 not aiming to study placebo/nocebo effects or not using learning to induce placebo/nocebo,
3721 not reporting original data or (full length, peer reviewed) experimental studies,
1197 not studying placebo/nocebo on humans,
139 being duplicates,
33 not studying cutaneous sensations,
70 not studying healthy participants,
13 not reported in English, German, or Dutch.
Records screened based on full text (n = 174)
Records excluded (n = 94) for the following reasons:
32 not aiming to study placebo/nocebo effects or not using learning to induce placebo/nocebo,
17 not reporting original data or (full length, peer reviewed) experimental studies,
35 not studying cutaneous sensations,
1 not studying healthy participants,
9 not reporting self-reported pain/itch ratings.
Studies included based on database searches (n = 80)
Articles identified in reference lists of studies (n = 2232)
Records excluded (n = 2212) for the following reasons:
1265 not aiming to study placebo/nocebo effects or not using learning to induce placebo/nocebo,
256 not reporting original data or (full length, peer reviewed) experimental studies,
565 being duplicates or already dealt with,
122 not studying healthy participants,
2 not reporting self-reported pain/itch ratings,
2 not having a control group or condition.
Studies included based on reference lists (n = 20)
Articles identified in Web of Science search of cited studies (n = 2123)
Records excluded (n = 2105) for the following reasons:
491 not aiming to study placebo/nocebo effects or not using learning to induce placebo/nocebo,
134 not reporting original data or (full length, peer reviewed) experimental studies,
1458 being duplicates or already dealt with,
4 not studying healthy participants,
4 not reporting self-reported pain/itch ratings.
Studies included based on Web of Science (n = 18)

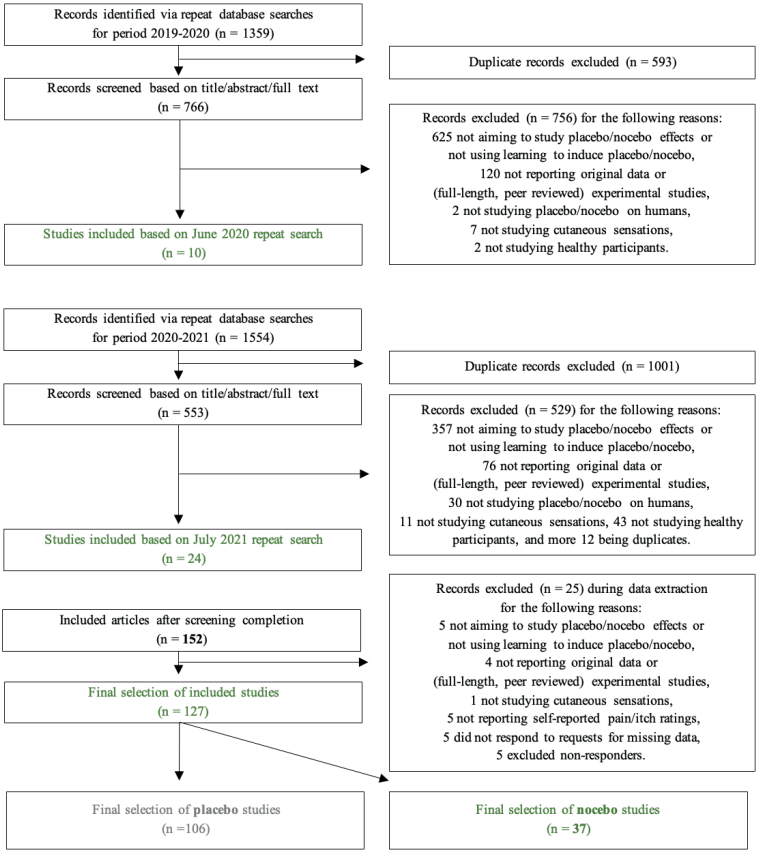


Figure 1. Flow diagram detailing the inclusion and exclusion of studies. The final sample included 127 articles, of which 106 investigated placebo effects, and 37 investigated nocebo effects (i.e., 16 studies overlapped as they investigated both placebo and nocebo).

Study characteristics

Table 1 displays study characteristics. We included 37 distinct nocebo studies, published between 2008 and 2021. Including additional

experimental conditions in a number of studies (see **Table 1**) in total we analyzed 40 study arms (30 pain and 10 itch). Thermal pain inductions were used in 19 arms, electrical pain was used in 6, pressure pain was used in 1, and mechanical, cold pressor, hot water bath, and histamine methods were each used in 1 study arm. Only 7 studies (10 arms) induced nocebo effects on itch, one of which also included pain (this study, van Laarhoven et al., 2011, is listed under *Pain* in **Table 1**). Electrical itch was used in 3 studies, one of which (van Laarhoven et al., 2011) used additional mechanical and histamine inductions in both the pain and itch groups (see **Table 1**). Histamine was used in 3 more itch studies and cowhage was used in 1 study.

For nocebo induction, most studies (18 pain and 4 itch studies) used a combination of classical conditioning and negative verbal suggestions, and for 3 we included additional study arms that employed verbal suggestions alone (**Table 1**). Verbal suggestions alone were used as the main manipulation in 10 pain studies (in total 12 arms) and 3 itch studies (in total 6 arms). Risk of bias was low within all studies, with most studies showing low risk of bias (max. 5/34) and only one study scoring in the low-moderate range with a score of 6/34 (**Table 1**). The funnel plots as well as a trim and fill method that suggested a small number of imputed studies (**Figure 3**) indicated that overall, there was a low degree of potential publication bias across all studies, with a total estimated 7 studies missing.

Magnitude of nocebo responses

See **Figures 2** and **3** for forest and funnel plots, respectively, that display effect sizes per study and pooled effects. For pain (**Figures 2A** and **2B**), the magnitude of nocebo responses on a standardized scale of 0-10 (with higher scores indicating larger nocebo magnitudes) across studies using classical conditioning with verbal suggestions ranged from 0.28 to 1.42, with the mean standardized response being M = **0.79** (SE = 0.24). Verbal suggestions alone induced effects on pain ranging from 0.00 to 1.27 (M = **0.70**, SE = 0.30). For itch, the magnitude of nocebo responses in studies that used conditioning with verbal suggestions ranged from 0.21 to 0.47 (M = **0.35**, SE = 0.24). Verbal suggestions alone induced effects on itch ranging from 0.41 to 0.75 (M = **0.58**, SE = 0.26). Based on these results, on average our meta-analysis indicated medium effects of the nocebo manipulations (Hedges g between 0.26-0.71 for each of the four pooled effects), a moderate degree of heterogeneity (I^2 average 41% across the four pooled effects), with the study effect sizes ranging between g = 0.00 and g = 1.34.

Table 1. Study characteristics for all included articles.

	Authors	Year	Sample size nocebo group	Sample size control group	Mean age (SD)	Stimulat. type	Learn. method	Results synthesis where applicable	Number of conditioning trials (N/C)	Risk of Bias score (0-34)
PAIN										
1	Colagiuri, Quinn, et al	**2015**	37	42	20.3 (4.0)	Electrical	CC+VS		32 (16/16)	3
2	Colagiuri & Quinn	**2018**	20	20	20.2 (4.0)	Electrical	CC+VS		32 (16/16)	5
3	Colagiuri, Park, et al.	**2021**	20 + 20	21 + 20	20.7 (3.6)	Electrical	CC+VS	Lengthier learning condition treated and analyzed as a separate study arm	32 (16/16)	3
4	Colloca, Petrovic, et al.	**2010**	23 + 23	n/a	22.8 (3.4)	Electrical	CC+VS	Four vs. of one learning sessions averaged together	20 (10/10) or 80 (40/40)	3
5	Colloca, Sigaudo, et al	**2008**	42 VS & 45 CC+VS	n/a	22.3 (2.4)	Electrical	CC+VS & VS	Three pain intensities averaged across VS and CC+VS conditions and analyzed as two separate study arms	24 (12/12)	3
	Corsi & Colloca	**2017**	46	n/a	27.4 (1.1)	Thermal	CC+VS		12 (6/6)	3
7	Egorova, Benedetti, et al	**2020**	24	n/a	n/a	Thermal	CC+VS		48 (24/24)	5
8	Feldhaus, Horing, et al.	**2021**	624	n/a	24.6 (3.6)	Thermal	CC+VS		16 (8/8)	3
9	Freeman, Yu, et al.	**2015**	24	n/a	21 to 49	Thermal	CC+VS		18 (9/9)	5
10	Geuter & Büchel	**2013**	20	n/a	26.4	Thermal	CC+VS		24 (12/12)	3
11	Kong, Gollub, et al.	**2008**	13	n/a	26.3 (3.6)	Thermal	CC+VS		48 (24/24)	5
12	Pazzaglia, Testani, et al.	**2016**	9 + 9	n/a	29 (5.0)	Laser	CC+VS &VS	VS condition treated and analyzed as a separate study arm	60 (30/30)	5

13	Skvortsova, Veldhuijzen, et al.	**2019**	37	n/a	23.1 (2.9)	Thermal	CC+VS		24 (12/12)	0
14	Thomaidou, Blythe, et al.	**2021b**	36	n/a	22.9 (2.2)	Thermal	CC+VS		32 (16/16)	5
15	Thomaidou, Veldhuijzen, et al.	**2020**	48	25	21.8 (2.1)	Thermal	CC+VS		30 (15/15)	5
16	Thomaidou, Veldhuijzen, et al.	**2021a**	24	n/a	22.2 (1.9)	Thermal	CC+VS		24 (12/12)	5
17	Tinnermann, Geuter, et al.	**2017**	25 + 24	n/a	25.4 (3.8)	Thermal	CC+VS	Cheap vs. expensive conditions were averaged together	16 (8/8)	6
18	Tu, Wilson, et al.	**2021**	27	n/a	27.4 (6.4)	Thermal	CC+VS		48 (24/24)	3
19	Wei, Zhou, et al.	**2018**	18	n/a	20.9 (1.4)	Electrical	CC+VS		40 (20/20)	3
20	Weng, Peerdeman, et al.	**2021**	33	n/a	21.6 (3.0)	Thermal	CC+VS		30 (15/15)	1
21	Albu & Meagher	**2016**	15	15	19.1 (1.2)	Thermal	VS		n/a	3
22	Aslaksen & Lyby	**2015**	57	54	22.2 (3.1)	Thermal	VS		n/a	3
23	Aslaksen, Åsli, et al.	**2016**	15	16	21.6 (3.3)	Thermal	VS		n/a	0
24	Aslaksen, Zwarg, et al.	**2015**	25	25	23.4 (4.1)	Thermal	VS		n/a	0
25	Camerone, Piedimonte, et al.	**2021**	19	21	23.1 (2.1)	Electrical	VS	We analyzed the 5-min condition	n/a	1
26	Geers, Close, et al.	**2019**	36	36	19.7 (3.2)	Cold pressor	VS		n/a	3
27	Nir, Yarnitsky, et al.	**2012**	12	12	25.8 (3.2)	Hot water bath	VS		n/a	3
28	van den Broeke, Geene, et al.	**2014**	15	15	23.5 (2.2)	Mechanical stimulation	VS		n/a	4
29	Vögtle, Barke, et al	**2013**	26	26	22.5 (4.4)	Pressure	VS		n/a	2
30-31	van Laarhoven, Vogelaar, et al.	**2011**	33pain & 36itch	16pain & 20itch	21.8 (2.2)	Electrical, Mechanical, Histamine	VS	Three types of stimulations averaged together across pain and across itch	n/a	1

ITCH										
32	Bartels, van Laarhoven, et al.	**2014**	23 + 23	25	22.7 (3.2)	Electrical	CC+VS & VS	VS condition treated and analyzed as a separate arm	12 (6/6)	4
33	Bartels, van Laarhoven, et al.	**2017**	99	n/a	20.3 (2.5)	Electrical	CC+VS		16 (10/6)	4
34	Blythe, Peerdeman, et al.	**2021**	19	19	21.9 (2.4)	Cowhage	CC+VS		4 (2/2)	2
35	van de Sand, Menz, et al.	**2018**	30	30	25.5	Histamine skin scrub	CC+VS		40 (20/20)	5
36	Meeuwis, van Middendorp, et al.	**2019**	24	n/a	21.8 (2.7)	Histamine iontophor.	VS		n/a	4
37	Meeuwis, van Middendorp, et al.	**2021**	28	n/a	21.9 (2.8)	Histamine iontophor.	VS		n/a	4

Note: the study by van Laarhoven et al., 2011, included both itch and pain manipulations and is listed under pain. When the sample size of a control group is listed as n/a, this suggests that the study used a within-subjects controlled design. Studies are listed separately for pain and itch and first based on the learning manipulation (VS, verbal suggestions, or CC+VS, combination of classical conditioning and verbal suggestions) and then alphabetically. N, Nocebo; C, Control; M, Male; F, Female.

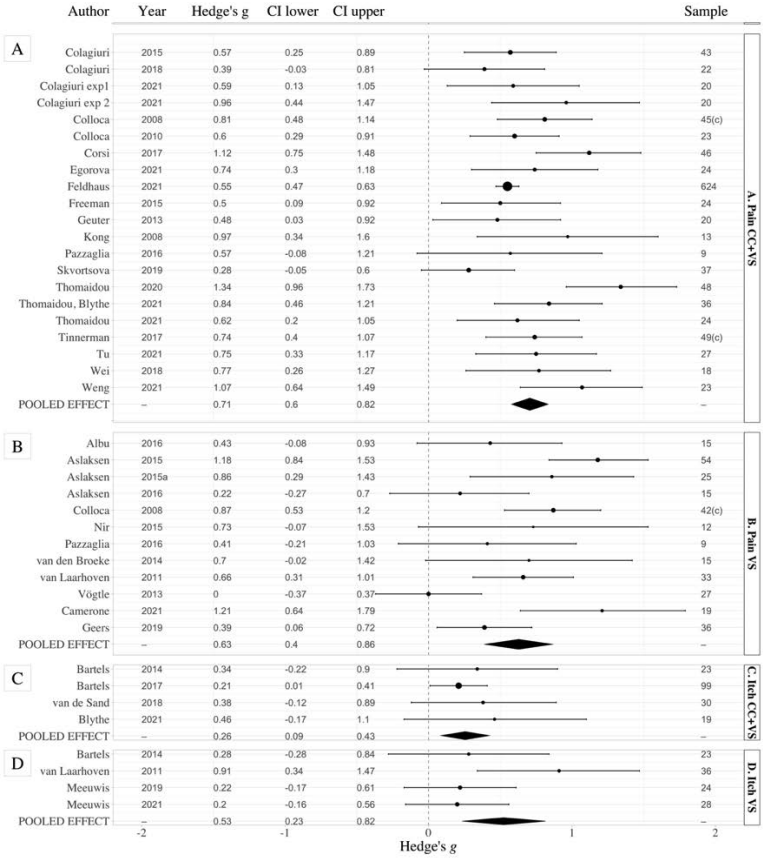


Figure 2. Forest plot of the meta-analysis indicating the magnitudes of nocebo responses following a combination of classical conditioning and verbal suggestions (CC+VS) or verbal suggestions alone (VS) on pain (**A, B**) and itch (**C, D**). Sample sizes marked with (c) indicate the combined sample from different study arms.

Classical conditioning and verbal suggestions in pain and itch

A range of different verbal suggestions were used to induce nocebo responses on pain and itch. Most studies used either an inert cream or inactive electrodes as the nocebo stimulus that would supposedly increase pain/itch sensitivity. For example, studies suggested to participants that their pain will be increased upon the activation of electrodes on their skin because these electrodes "enhance the conductivity of the pain signal being sent to the brain" [29] or "the cream that will be applied to your arm increases the effect of the heat pain and you will feel more pain after the application." [17]. Most such suggestions were delivered orally by a researcher, with few studies providing such information in writing [9,21,29–31].

For **pain**, a somewhat larger pooled nocebo effect of the combination of **conditioning with verbal suggestions** (k = 21, g = **0.71**, 95% CI 0.60 – 0.82, I^2 = 50.71%; **Figure 2A**) was observed than of **verbal suggestions** alone (k = 12, g = **0.63**, 95% CI 0.40 – 0.86, I^2 = 55.59%; **Figure 2B**). In **itch**, however, **conditioning with verbal suggestions** yielded a smaller pooled effect on the magnitude of nocebo responses (k = 4, g = **0.26**, 95% CI 0.09 – 0.43, I^2 = 0%; **Figure 2C**) compared to a medium pooled effect of **verbal suggestions** alone (k = 4, g = **0.53**, 95% CI 0.23 – 0.82, I^2 = 53.81%; **Figure 2D**) on nocebo responses. Overall, nocebo responses (see Table 1 for the relevant studies) were thus associated with medium pooled effects in pain, while in itch they were associated with slightly smaller pooled effects overall.

Magnitude of nocebo responses based on the type of stimulation

For **pain** studies that used **conditioning with verbal suggestions**, we compared effects of different pain administration methods (k = 13 thermal, k = 7 electrical) excluding the single study using laser. Thermal

pain yielded a somewhat larger pooled effect on the magnitude of nocebo responses (k = 13, g = 0.75, 95% CI 0.59 – 0.91) compared to medium pooled effects of electrical pain (k = 7, g = 0.65, 95% CI 0.51 – 0.79) on nocebo responses. For **pain** studies that used only **verbal suggestions**, we examined effects of different pain administration methods (k = 4 thermal, k = 5 electrical, k = 2 mechanical) excluding the single studies using laser, cold pressor, hot water bath, pressure, and histamine. Electrical pain yielded slightly larger pooled effect on the magnitude of nocebo responses (k = 5, g = 0.91, 95% CI 0.65 – 1.17) compared to medium effects of thermal (k = 4, g = 0.69, 95% CI 0.21 – 1.16) and mechanical (k = 2, g = 0.60, 95% CI 0.14 – 1.06).

For **itch** studies that used **conditioning with verbal suggestions**, there were too few studies to analyze (cowhage k = 1, electrical itch k = 2, and histamine k = 1). For **itch** studies that used only **verbal suggestions**, there were again too few studies (k = 2 electrical, k = 3 histamine, k = 1 mechanical).

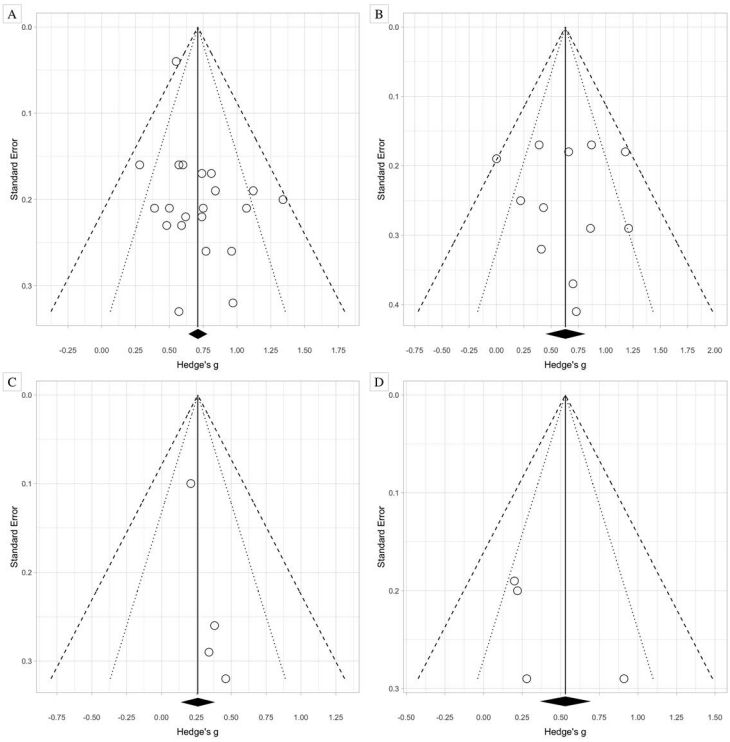


Figure 3. Funnel plots displaying studies within and outside of 95% (dotted line) and 99% (dashed line) CI, for pain verbal suggestions with (A) and without (B) conditioning, and for itch verbal suggestions with (A) and without (B) conditioning.

Magnitude of nocebo hyperalgesia based the timing of measurement

All itch conditioning studies measured the nocebo effect as the mean of all evocation trials. Among **pain** studies that employed a combination of **conditioning with verbal suggestion**, however, 13 paradigms

measured nocebo responses as the mean of all evocation (testing) trials, 6 measured the magnitude of responses in the first pair of evocation trials, and 2 studies specified different timing such as pre-post measures. Studies in which first evocation trials were used yielded a large pooled effect on the magnitude of nocebo responses (k = 6, g = 0.82, 95% CI 0.57 – 1.07) compared to medium pooled effects of measuring the effect as the mean of all evocation trials (k = 13, g = 0.66, 95% CI 0.54 – 0.79) and non-specified (k = 2, g = 0.67, 95% CI 0.23 – 1.11).

Magnitude of nocebo hyperalgesia based on the number of learning trials

Studies that employed **classical conditioning** used varying numbers of learning and evocation trials. For **pain only**, there were sufficient studies to examine the effects of different lengths of conditioning and different lengths of evocation (i.e., the length of extinction) on nocebo magnitudes. The shortest pain learning paradigm used 6 nocebo and 6 control trials, while the longest paradigms used up to 30 nocebo and 30 control trials. Evocation phases ranged from 3 nocebo and 3 control trials to 30 nocebo and 30 control trials. A meta-regression of different lengths of conditioning showed no association with the magnitude of nocebo responses (Q = 0.81, p = 0.37). Similarly, there was no association between the length of evocation and nocebo magnitudes (Q = 0.19, p = 0.67).

Magnitude of nocebo hyperalgesia based on the pain stimulus intensity

For **pain** studies that employed **classical conditioning with verbal suggestions** we had a sufficient sample to examine any relationship between differences in intensity of pain stimulations in the learning

phase and the magnitude of nocebo responses, but a meta-regression found no significant association ($Q = 0.89$, $p = 0.35$).

Magnitude of nocebo responses based on the Risk of Bias score

Lastly, we examined how RoB scores may be related to nocebo magnitudes. A meta-regression showed no significant relationship between RoB scores and the magnitude of nocebo responses for **pain** studies that used **conditioning and verbal suggestions** ($Q = 0.75$, $p = 0.39$), for **pain** studies that used only **verbal suggestions** ($Q = 0.00$, $p = 0.95$), for **itch** studies that used **conditioning and verbal suggestions** ($Q = 0.08$, $p = 0.77$), or for **itch** studies that used **verbal suggestions** alone ($Q = 1.9$, $p = 0.05$).

Discussion

We conducted a systematic review and meta-analysis of a total of 37 distinct nocebo studies on healthy participants. This meta-analysis showed that on average, nocebo effects were moderate to large in magnitude. The combination of verbal suggestions with classical conditioning yielded stronger nocebo responses on pain, but this may not necessarily be the case in the small number of itch studies. Measures of the type or intensity of pain or itch, and length of learning, did not explain the moderate heterogeneity in nocebo magnitudes between different studies. Timing of nocebo measurement in the first evocation trials yielded slightly larger nocebo magnitudes. Risk of bias was

generally low and was not related to nocebo magnitudes either. We discuss these results in relation to the role of conditioning as well as aversive learning, and we speculate of the reasons why none of the factors collected in the nocebo literature appear to consistently explain variations in the magnitudes of learned nocebo effects on pain and itch.

In experimental inductions of nocebo effects on pain, we found the magnitudes of responses across studies to be moderate to large, with a moderate heterogeneity. Often conceptualized as the counterpart of nocebo responses, placebo effects appear to be comparable in magnitude to the overall nocebo magnitude found in the current meta-analysis, but heterogeneity in placebo responses may be higher [19]. In a more recent meta-analysis, placebo responses were found to yield small to moderate effects, with moderate to large heterogeneity in results [32]. We speculate that this may indicate that the negativity of suggestions and experiences in nocebo paradigms may result in stronger learned effects, as compared to the positive expectations induced in placebo excrements. Indeed, aversive learning has consistently be shown to be prioritized over the learning of neutral or positive information in the brain [33–36], something that is thought to have an evolutionary basis [37].

Magnitudes of nocebo responses were found to be moderate to large in pain studies when looking at both verbal suggestions and combination with conditioning. As expected, in pain experiments the addition of classical conditioning yielded somewhat larger nocebo responses, suggesting that learning by experience during behavioral conditioning may be more potent than mere negative suggestions regarding pain outcomes. For itch, however, verbal suggestions alone yielded moderate effects whereas combination with conditioning resulted in small effects across studies. The number of studies included in each of the two itch conditions (k = 4 in each) may be insufficient to allow for further conclusions to be drawn regarding this apparent distinction between learned pain and itch effects.

While the number of itch studies included in this meta-analysis was small (8) compared to pain (30), overall effects on pain appear to be larger than those on itch across both learning methods, based on the present findings. Itch has been shown to be prone to suggestions and can be influenced by expectations [4] with one study that compared placebo effects induced with verbal suggestions for either pain or itch indicating that itch might be more prone to suggestions [38]. Our finding that pain resulted in larger nocebo magnitudes across the studies included here, could suggest that compared to itch, the learning of pain associations may be facilitated to a larger degree. In other words, we speculate that, as pain is perhaps more threatening and aversive than itch, it may signal a more vital threat to the person and thereby, from an evolutionary perspective [37], result in stronger learning. Further research into nocebo effects is needed, however, to reach a sufficient sample size for reliable comparison results between pain and itch.

The variability found in nocebo response magnitudes was not explained by differences between the type or intensity of pain or itch stimulation, or the length of learning. A moderate dispersion of effect sizes across the studies analyzed is important to note, especially when the measures that are systematically reported in studies, such as the duration of learning or the intensity of pain, are unable to explain such variability in nocebo response magnitudes. The large differences in applied experimental models of nocebo effects (e.g., different types of verbal suggestions, whether the experiment was conducted in a hospital or university setting, or types of nocebo and conditioned stimuli presented) may explain some of this variability in results [39]. Similarly to the efforts for aligning experimental paradigms in animal models of disease [40,41], it is essential for the field of nocebo to focus on replicating experimental paradigms and aligning paradigms according to ecologically valid models that yield comparable results across studies.

One of the most consistent differences between experimental nocebo studies seems to be the type of verbal suggestion delivered to participants. No two studies administered the same verbal suggestion. Different verbal suggestions could contain distinct emotional loads and be perceived as more or less threatening, which may in turn influence nocebo responses [13,17]. While beyond the scope and reach of the current meta-analysis, a future systematic review of distinct verbal suggestions, for example using content analysis approaches borrowed from linguistics [42,43], could shed a light on how different verbal suggestions could impact nocebo responses.

There are other variables that could explain variability of induced nocebo responses, such as sampling, demographics, and the inclusion criteria for participation, but a limitation is that these factors are not consistently reported in papers and could not be investigated in the current meta-analysis. Additionally, studies do not systematically measure fear, which is shown repeatedly to be involved in nocebo responses [13,17,44–46]. Other variables relevant to the emotional context of studies, such as the demeanor of the experimenter [47] or whether the experiment is set in an academic building or hospital, are also often not clearly documented, and could not be analyzed here. Finally, risk of bias was low across all studies and showed no relationship to nocebo magnitudes. However, the assessment tool used for this meta-analysis is designed for quantitative sensory testing studies [23] but could have missed bias aspects, such as potential publication bias for significant results, which meta-analyses studies should consider addressing.

This systematic review and meta-analysis quantified magnitudes of nocebo responses on cutaneous sensations (pain and itch) for distinct learning paradigms in experimental studies (classical conditioning with verbal suggestion, or verbal suggestion alone). We replicated previous findings that classical conditioning combined with negative verbal suggestions was strongest for inducing nocebo responses on pain.

Subgroup analyses indicated that factors related to the length of learning paradigms or intensity and type of sensory stimuli did not explain the moderate heterogeneity in nocebo effect sizes. This review provides a comprehensive summary of current findings in the field of nocebo research. We have ruled out some factors that were consistently reported in papers and could not explain the variability in results across studies, and we recommended some important directions for the field, such as increased consistency between study designs for inducing nocebo effects, as well as a systematic examination of the effects of different verbal suggestions on magnitudes of learned nocebo effects.

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