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

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Citation

Thomaidou, A. M. (2022, September 7). *How negative experiences influence the brain in pain: neuroimaging and biobehavioral insights*. Retrieved from <https://hdl.handle.net/1887/3455208>

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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 placebo 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 placebo effects and the factors that contribute to their formation will help steer placebo 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 placebo studies on healthy participants, with four separate meta-analyses for placebo 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 placebo 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 placebo responses on pain in particular. Subgroup analyses, including factors such as the type of sensory stimulation, did not explain the moderate heterogeneity in placebo magnitudes between different studies. Risk of bias was generally low and was not related to placebo 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 placebo 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 placebo effects lead to symptom amplification ^{4–10}. In experimental studies, placebo responses are defined as a significant increase in a sensation after a placebo 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 placebo 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 placebo studies employ diverse methods, to better understand their potential impact on placebo outcomes these methodological features warrant a systematic investigation.

Learning has consistently been shown to underlie induced placebo effects ^{5–7,9,17}, and verbal suggestions seem to induce stronger placebo responses when combined with conditioning ¹⁸. The positive counterpart to placebo, 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 placebo experiments published up to 2013 and reports that the overall magnitude of the placebo 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 placebo 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 placebo research, some placebo 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 placebo experiments, can potentially influence placebo responding and thus merit further investigation.

Given the recent growth of placebo research, we conducted a systematic review and meta-analysis of experimental placebo studies in healthy participants to provide novel insights into distinct contributions of methodological factors in the induction of placebo responses. We focused on cutaneous sensations, aiming to examine placebo responses induced with comparable sensory inductions externally on the skin. First, we examined placebo 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 placebo magnitudes, and risk of bias in studies may impact placebo 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 placebo and placebo studies, which, due to the volume of the studies returned, is now divided in two separate papers. Here, we report only the placebo (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 placebo 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 inverting 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 placebo and control conditions based on what was reported in studies: some reported placebo 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 imputed²⁸. 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 placebo 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 placebo 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 placebo 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. placebo trials) and the Risk of Bias score on placebo magnitudes for the included studies.

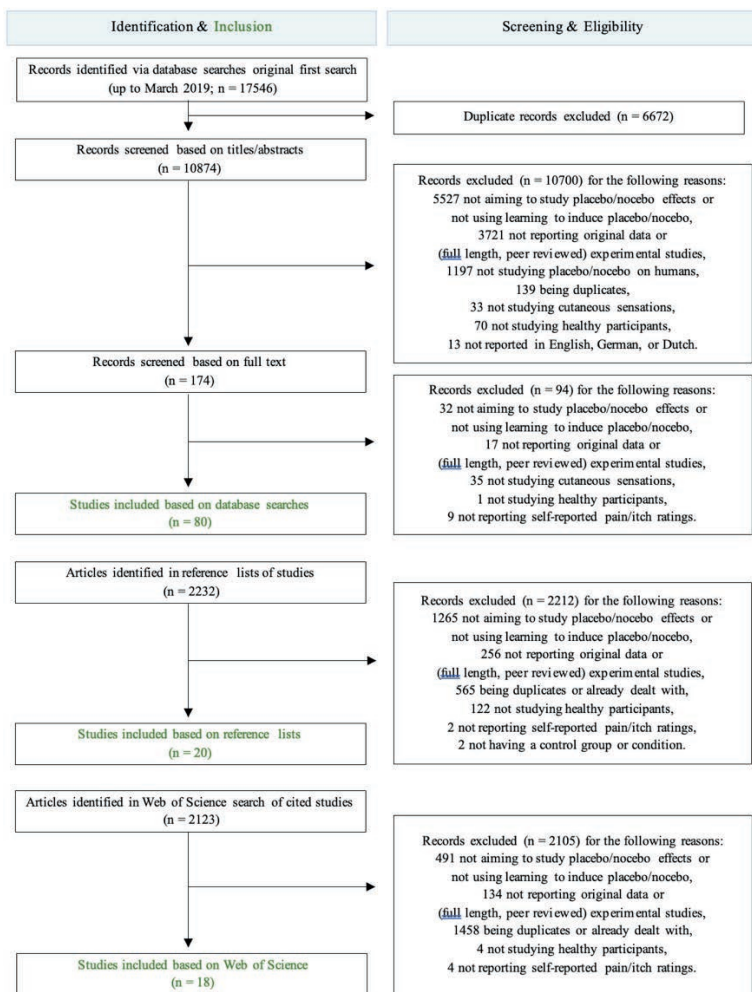
Results

Study selection

Figure 1 shows the flow of the study selection process including the reasons for exclusion at each stage. A total of 17546 placebo 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.



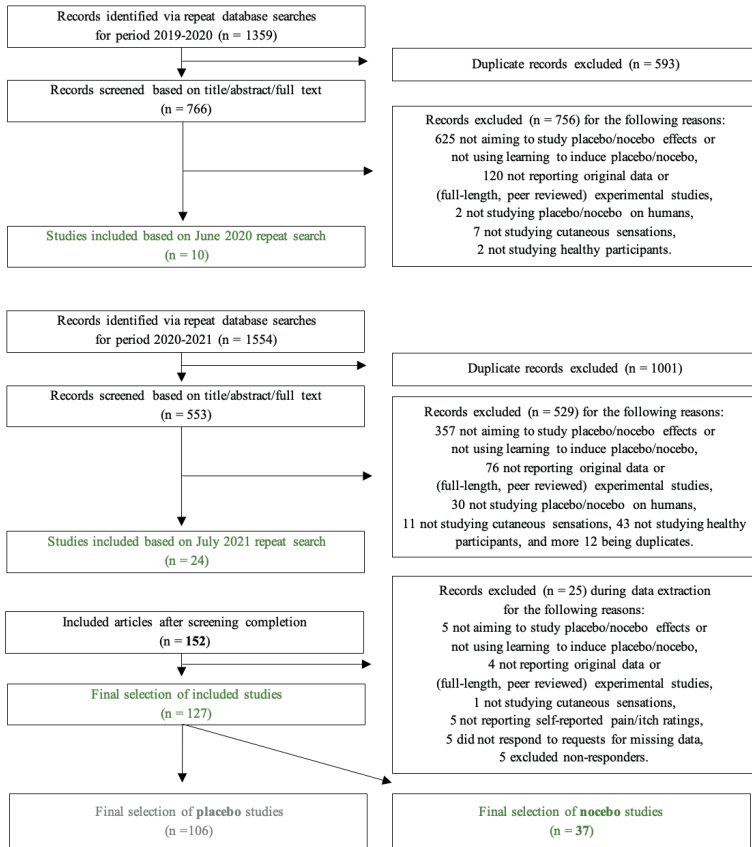


Figure 1. Flow diagram detailing the inclusion and exclusion of studies. The final sample included 127 articles, of which 106 investigated placebo effects, and 37 investigated nocebo effects (i.e., 16 studies overlapped as they investigated both placebo and nocebo).

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 placebo 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 placebo 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 placebo 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 placebo responses on a standardized scale of 0-10 (with higher scores indicating larger placebo 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 placebo 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 placebo 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. metho d	Results synthesis where applicable	Number of condition ing trials (N/C)	Ris k of Bias score (0- 34)
PAIN										
1	Colagiuri, Quinn, et al	2015	37	42	20.3 (4.0)	Electrical	CC+V S		32 (16/16)	3
2	Colagiuri & Quinn	2018	20	20	20.2 (4.0)	Electrical	CC+V S		32 (16/16)	5
3	Colagiuri, Park, et al.	2021	20 + 20	21 + 20	20.7 (3.6)	Electrical	CC+V S	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+V S	Four vs. of one learning sessions averaged together	20 (10/10) or 80 (40/40)	3
5	Colloca, Sigaud, et al	2008	42 VS & 45 CC+VS	n/a	22.3 (2.4)	Electrical	CC+V S & 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+V S		12 (6/6)	3
7	Egorova, Benedetti, et al	2020	24	n/a	n/a	Thermal	CC+V S		48 (24/24)	5
8	Feldhaus, Horing, et al.	2021	624	n/a	24.6 (3.6)	Thermal	CC+V S		16 (8/8)	3
9	Freeman, Yu, et al.	2015	24	n/a	21 to 49	Thermal	CC+V S		18 (9/9)	5
10	Geuter & Büchel	2013	20	n/a	26.4	Thermal	CC+V S		24 (12/12)	3
11	Kong, Gollub, et al.	2008	13	n/a	26.3 (3.6)	Thermal	CC+V S		48 (24/24)	5
12	Pazzaglia, Testani, et al.	2016	9 + 9	n/a	29 (5.0)	Laser	CC+V S & VS	VS condition treated and analyzed as a separate study arm	60 (30/30)	5

13	Skvortsov a, Veldhuijzen, et al.	2019	37	n/a	23.1 (2.9)	Thermal	CC+V S	24 (12/12)	0
14	Thomaïdou, Blythe, et al.	2021 b	36	n/a	22.9 (2.2)	Thermal	CC+V S	32 (16/16)	5
15	Thomaïdou, Veldhuijzen, et al.	2020	48	25	21.8 (2.1)	Thermal	CC+V S	30 (15/15)	5
16	Thomaïdou, Veldhuijzen, et al.	2021 a	24	n/a	22.2 (1.9)	Thermal	CC+V S	24 (12/12)	5
17	Tinnermann, Geuter, et al.	2017	25 + 24	n/a	25.4 (3.8)	Thermal	CC+V S	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+V S	48 (24/24)	3
19	Wei, Zhou, et al.	2018	18	n/a	20.9 (1.4)	Electrical	CC+V S	40 (20/20)	3
20	Weng, Peerdeman, et al.	2021	33	n/a	21.6 (3.0)	Thermal	CC+V S	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, Asli, 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, Piedmonte, 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										
3 2	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
3 3	Bartels, van Laarhoven, et al.	2017	99	n/a	20.3 (2.5)	Electrical	CC+VS		16 (10/6)	4
3 4	Blythe, Peerdeman, et al.	2021	19	19	21.9 (2.4)	Cowhage	CC+VS		4 (2/2)	2
3 5	van de Sand, Menz, et al.	2018	30	30	25.5	Histamine skin scrub	CC+VS		40 (20/20)	5
3 6	Meeuwis, van Middendorp, et al.	2019	24	n/a	21.8 (2.7)	Histamine iontophore	VS		n/a	4
3 7	Meeuwis, van Middendorp, et al.	2021	28	n/a	21.9 (2.8)	Histamine iontophore	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.

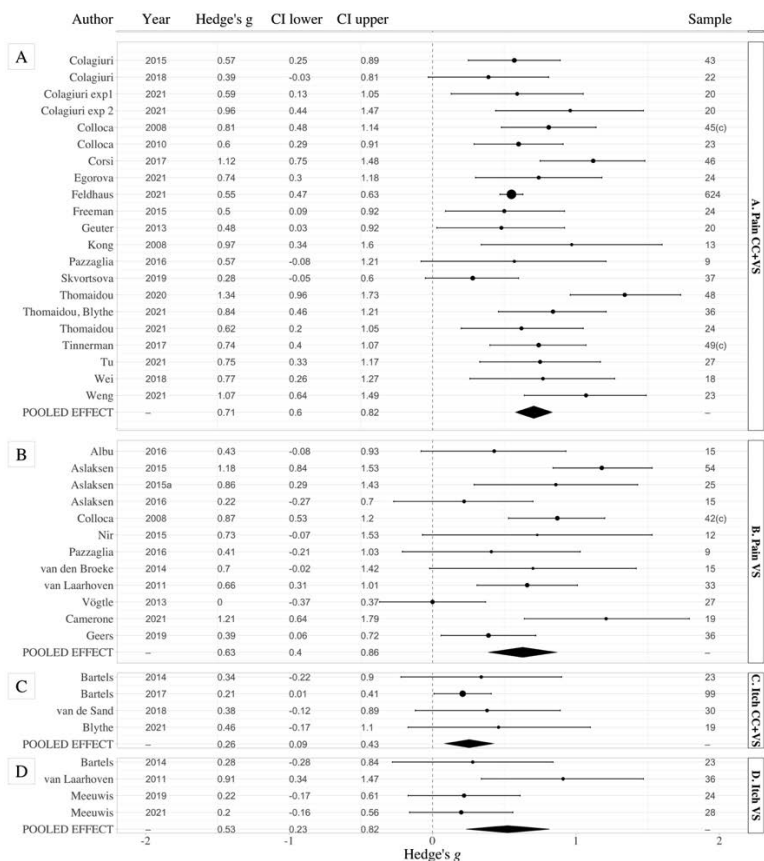


Figure 2. Forest plot of the meta-analysis indicating the magnitudes of nocebo responses following a combination of classical conditioning and verbal suggestions (CC+VS) or verbal suggestions alone (VS) on pain (**A, B**) and itch (**C, D**). Sample sizes marked with (c) indicate the combined sample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

Classical conditioning and verbal suggestions in pain and itch

A range of different verbal suggestions were used to induce placebo responses on pain and itch. Most studies used either an inert cream or inactive electrodes as the placebo 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 placebo 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 placebo 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 placebo responses. Overall, placebo 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 placebo 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 ($k = 13, g = 0.75, 95\% \text{ CI } 0.59 - 0.91$) compared to medium pooled effects of electrical pain ($k = 7, g = 0.65, 95\% \text{ CI } 0.51 - 0.79$) 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 ($k = 5, g = 0.91, 95\% \text{ CI } 0.65 - 1.17$) compared to medium effects of thermal ($k = 4, g = 0.69, 95\% \text{ CI } 0.21 - 1.16$) and mechanical ($k = 2, g = 0.60, 95\% \text{ CI } 0.14 - 1.06$).

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).

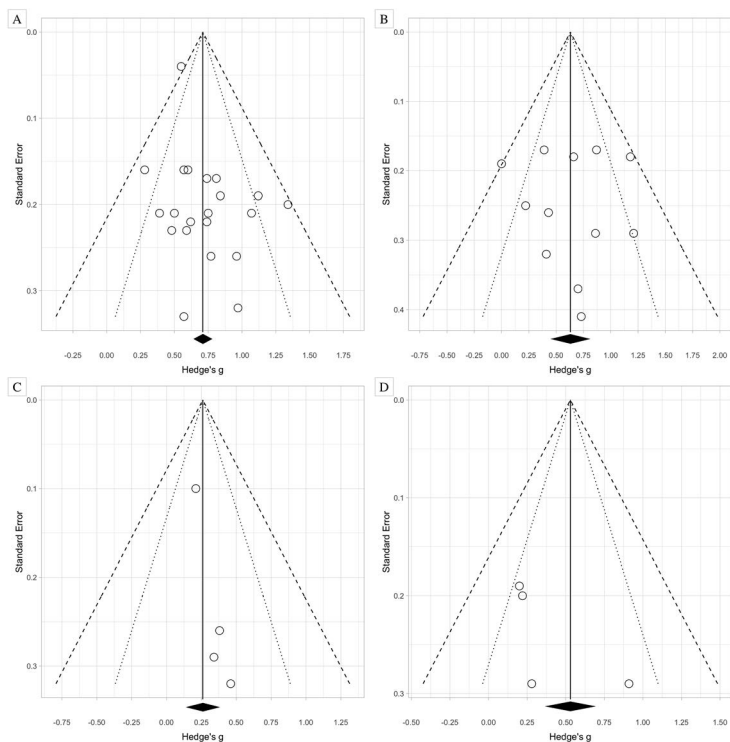


Figure 3. Funnel plots displaying studies within and outside of 95% (dotted line) and 99% (dashed line) CI, for pain verbal suggestions with (A) and without (B) conditioning, and for itch verbal suggestions with (A) and without (B) conditioning.

Magnitude of placebo hyperalgesia based the timing of measurement

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

measured placebo 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 placebo responses ($k = 6, g = 0.82, 95\% \text{ CI } 0.57 - 1.07$) compared to medium pooled effects of measuring the effect as the mean of all evocation trials ($k = 13, g = 0.66, 95\% \text{ CI } 0.54 - 0.79$) and non-specified ($k = 2, g = 0.67, 95\% \text{ CI } 0.23 - 1.11$).

Magnitude of placebo 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 placebo magnitudes. The shortest pain learning paradigm used 6 placebo and 6 control trials, while the longest paradigms used up to 30 placebo and 30 control trials. Evocation phases ranged from 3 placebo and 3 control trials to 30 placebo and 30 control trials. A meta-regression of different lengths of conditioning showed no association with the magnitude of placebo responses ($Q = 0.81, p = 0.37$). Similarly, there was no association between the length of evocation and placebo magnitudes ($Q = 0.19, p = 0.67$).

Magnitude of placebo 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 placebo responses, but a meta-regression found no significant association ($Q = 0.89, p = 0.35$).

Magnitude of placebo responses based on the Risk of Bias score

Lastly, we examined how RoB scores may be related to placebo magnitudes. A meta-regression showed no significant relationship between RoB scores and the magnitude of placebo 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 placebo studies on healthy participants. This meta-analysis showed that on average, placebo effects were moderate to large in magnitude. The combination of verbal suggestions with classical conditioning yielded stronger placebo 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 placebo magnitudes between different studies. Timing of placebo measurement in the first evocation trials yielded slightly larger placebo 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 placebo 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 placebo 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 placebo responses.

There are other variables that could explain variability of induced placebo 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 placebo responses^{13,17,44–46}. Other variables relevant to the emotional context of studies, such as the demeanor of the experimenter⁴⁷ 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 placebo magnitudes. However, the assessment tool used for this meta-analysis is designed for quantitative sensory testing studies²³ 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 placebo 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 placebo 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 placebo effect sizes. This review provides a comprehensive summary of current findings in the field of placebo 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 placebo effects, as well as a systematic examination of the effects of different verbal suggestions on magnitudes of learned placebo effects.

References

1. Barsky AJ. Nonspecific Medication Side Effects and the Nocebo Phenomenon. *JAMA*. 2002;287(5):622-627. doi:10.1001/jama.287.5.622
2. Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: Unraveling the mechanisms of the nocebo effect. *Neuroscience*. 2007;147(2):260-271. doi:10.1016/j.neuroscience.2007.02.020
3. Evers AWM, Peerdeman KJ, van Laarhoven AIM. What is new in the psychology of chronic itch? *Exp Dermatol*. 2019;28(12):1442-1447. doi:10.1111/exd.13992
4. Bartels DJP, van Laarhoven AIM, Haverkamp EA, et al. Role of Conditioning and Verbal Suggestion in Placebo and Nocebo Effects on Itch. Sakakibara M, ed. *PLoS ONE*. 2014;9(3):e91727. doi:10.1371/journal.pone.0091727
5. Blythe J, Peerdeman K, Veldhuijzen D, et al. Nocebo Effects on Cowhage-evoked Itch: A Randomized Controlled Trial of Classical Conditioning and Observational Learning. *Acta Derm Venereol*. 2021;101(1):adv00370. doi:10.2340/00015555-3723
6. Colagiuri B, Quinn VF, Colloca L. Nocebo Hyperalgesia, Partial Reinforcement, and Extinction. *The Journal of Pain*. 2015;16(10):995-1004. doi:10.1016/j.jpain.2015.06.012
7. Colloca L, Sigauco M, Benedetti F. The role of learning in nocebo and placebo effects. *Pain*. 2008;136(1):211-218. doi:10.1016/j.pain.2008.02.006
8. Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F. How the number of learning trials affects placebo and nocebo responses. *Pain*. 2010;151(2):430-439. doi:10.1016/j.pain.2010.08.007
9. Thomaidou MA, Veldhuijzen DS, Peerdeman KJ, Wiebing NZS, Blythe JS, Evers AWM. Learning mechanisms in nocebo hyperalgesia: the role of conditioning and extinction processes. *Pain*. 2020;161(7):1597-1608. doi:10.1097/j.pain.0000000000001861
10. Tu Y, Park J, Ahlfors SP, et al. A neural mechanism of direct and observational conditioning for placebo and nocebo responses. *NeuroImage*. Published online 2019. doi:10.1016/j.neuroimage.2018.10.020
11. Benedetti F, Durando J, Vighetti S. Nocebo and placebo modulation of hypobaric hypoxia headache involves the cyclooxygenase-prostaglandins pathway. *Pain*. 2014;155(5):921-928. doi:10.1016/j.pain.2014.01.016
12. Hird EJ, Jones AKP, Talmi D, El-Dereby W. A comparison between the neural correlates of laser and electric pain stimulation and their modulation by expectation. *Journal of Neuroscience Methods*. 2018;293:117-127. doi:10.1016/j.jneumeth.2017.09.011
13. Thomaidou MA, Veldhuijzen DS, Meulders A, Evers AWM. An experimental investigation into the mediating role of pain-related fear in boosting nocebo hyperalgesia. *Pain*. 2021;162(1):287-299. doi:10.1097/j.pain.0000000000002017
14. Stockhorst U. Classical conditioning of endocrine effects : Current Opinion in Psychiatry. *Current Opinion in Psychiatry*. 2005;18(2).
15. Reicherts P, Gerdes ABM, Pauli P, Wieser MJ. Psychological Placebo and Nocebo Effects on Pain Rely on Expectation and Previous Experience. Published online 2016. doi:10.1016/j.jpain.2015.10.010
16. Bräscher AK, Witthöft M, Becker S. The Underestimated Significance of Conditioning in Placebo Hypoalgesia and Nocebo Hyperalgesia. *Pain Research and Management*. 2018;2018:1-8. doi:10.1155/2018/6841985

17. Aslaksen PM, Lyby PS. Fear of pain potentiates placebo hyperalgesia. *Journal of pain research*. 2015;8:703-710. doi:10.2147/JPR.S91923
18. Petersen GL, Finnerup NB, Colloca L, et al. The magnitude of placebo effects in pain: A meta-analysis. *PAIN®*. 2014;155(8):1426-1434. doi:10.1016/J.PAIN.2014.04.016
19. Vase L, Riley JL, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain*. 2002;99(3):443-452. doi:10.1016/S0304-3959(02)00205-1
20. Blythe JS, Peerdeman KJ, Veldhuijzen DS, van Laarhoven AIM, Evers AWM. Placebo and placebo effects on itch: A review of experimental methods. *Itch*. 2019;4(3):e27. doi:10.1097/itx.0000000000000027
21. Kong J, Gollub RL, Polich G, et al. A Functional Magnetic Resonance Imaging Study on the Neural Mechanisms of Hyperalgesic Placebo Effect. *Journal of Neuroscience*. 2008;28(49):13354-13362-13354-13362. doi:10.1523/JNEUROSCI.2944-08.2008
22. Pazzaglia C, Testani E, Giordano R, Padua L, Valeriani M. Expectation to feel more pain disrupts the habituation of laser-pain rating and laser-evoked potential amplitudes. *Neuroscience*. 2016;333:244-251-244-251. doi:10.1016/j.neuroscience.2016.07.027
23. Marcuzzi A, Dean CM, Hush JM. Early changes in somatosensory function in spinal pain: protocol for a systematic review. *Systematic reviews*. 2013;2:90. doi:10.1186/2046-4053-2-90
24. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Published online 2019. <http://www.r-project.org/>
25. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463. doi:10.1111/j.0006-341x.2000.00455.x
26. Hak T, van Rhee H, Suurmond R. How to interpret results of meta-analysis. Rotterdam, The Netherlands: Erasmus Rotterdam Institute of Management. 2016;SSRN 3241367. www.crim.eur.nl/research-support/meta-essentials/downloads
27. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557
28. Peerdeman KJ, van Laarhoven AIM, Keij SM, et al. Relieving patients' pain with expectation interventions: a meta-analysis. *Pain*. 2016;157(6):1179-1191. doi:10.1097/j.pain.0000000000000540
29. Colagiuri B, Quinn VF. Autonomic Arousal as a Mechanism of the Persistence of Placebo Hyperalgesia. *The journal of pain: official journal of the American Pain Society*. 2018;19(5):476-486. doi:10.1016/j.jpain.2017.12.006
30. Vögtle E, Barke A, Kröner-Herwig B. Placebo hyperalgesia induced by social observational learning. *Pain*. 2013;154(8):1427-1433. doi:10.1016/j.pain.2013.04.041
31. Weng L, Peerdeman K, Della Porta D, Laarhoven AIM, Evers A. Can placebo and placebo effects generalize within pain modalities and across somatosensory sensations? *Pain*. 2021; Publish Ahead of Print. doi:10.1097/j.pain.0000000000002390
32. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev*. 2010;2010(1):CD003974. doi:10.1002/14651858.CD003974.pub3
33. Fullana MA, Harrison BJ, Soriano-Mas C, et al. Neural signatures of human fear conditioning: An updated and extended meta-analysis of fMRI studies. *Molecular Psychiatry*. 2016;21(4):500-508. doi:10.1038/mp.2015.88

34. Boddez Y, Moors A, Mertens G, De Houwer J. Tackling fear: Beyond associative memory activation as the only determinant of fear responding. *Neuroscience & Biobehavioral Reviews*. 2020;112:410-419. doi:10.1016/j.neubiorev.2020.02.009
35. Mechias ML, Etkin A, Kalisch R. A meta-analysis of instructed fear studies: Implications for conscious appraisal of threat. *NeuroImage*. 2010;49(2):1760-1768. doi:10.1016/j.neuroimage.2009.09.040
36. Kahneman D, Tversky A. The Psychology of Preferences. *Scientific American*. 1982;246(1):160-173.
37. Ohman A, Mineka S. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. *Psychological review*. 2001;108(3):483-522.
38. Van Laarhoven AIM, Vogelaar ML, Wilder-Smith O, et al. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. *Pain*. 2011;152(7):1486-1494. doi:10.1016/j.pain.2011.01.043
39. Thomaidou MA, Peerdeman KJ, Koppeschaar MI, Evers AWM, Veldhuijzen DS. How Negative Experience Influences the Brain: A Comprehensive Review of the Neurobiological Underpinnings of Nocebo Hyperalgesia. *Frontiers in Neuroscience*. 2021;15. doi:10.3389/fnins.2021.652552
40. Jones C, Watson D, Fone K. Animal models of schizophrenia. *Br J Pharmacol*. 2011;164(4):1162-1194. doi:10.1111/j.1476-5381.2011.01386.x
41. Lu Y, Yin DM, Xiong WC, Mei L. Modeling Schizophrenia in Neuregulin 1 and ErbB4 Mutant Mice. In: O'Donnell P, ed. *Animal Models of Schizophrenia and Related Disorders*. Neuromethods. Humana Press; 2011:261-277. doi:10.1007/978-1-61779-157-4_12
42. Ben-David BM, Moral MI, Namasivayam AK, Erel H, van Lieshout PHHM. Linguistic and emotional-valence characteristics of reading passages for clinical use and research. *Journal of Fluency Disorders*. 2016;49:1-12. doi:10.1016/j.jfludis.2016.06.003
43. Shaikh MAM, Prendinger H, Ishizuka M. Sentiment Assessment of Text by Analyzing Linguistic Features and Contextual Valence Assignment. *Applied Artificial Intelligence*. 2008;22(6):558-601. doi:10.1080/08839510802226801
44. Jensen K, Kaptchuk TJ, Chen X, et al. A neural mechanism for nonconscious activation of conditioned placebo and nocebo responses. *Cerebral Cortex*. 2015;25(10):3903-3910. doi:10.1093/cercor/bhu275
45. Schmid J, Bingel U, Ritter C, et al. Neural underpinnings of nocebo hyperalgesia in visceral pain: A fMRI study in healthy volunteers. *NeuroImage*. 2015;120:114-122-114-122. doi:10.1016/j.neuroimage.2015.06.060
46. Tinnermann A, Geuter S, Sprenger C, Finsterbusch J, Büchel C. Interactions between brain and spinal cord mediate value effects in nocebo hyperalgesia. *Science*. 2017;358:105-108.

References of the 37 studies included in this meta-analysis

- Albu, S., & Meagher, M. W. (2016). Expectation of nocebo hyperalgesia affects EEG alpha-activity. *International Journal of Psychophysiology*, 109, 147–152. <https://doi.org/10.1016/j.jpsycho.2016.08.009>
- Aslaksen, P. M., Åsli, O., Øvervoll, M., & Bjørkedal, E. (2016). Nocebo hyperalgesia and the startle response. *Neuroscience*, 339, 599–607. <https://doi.org/10.1016/j.neuroscience.2016.10.040>
- Aslaksen, P. M., & Lyby, P. S. (2015). Fear of pain potentiates nocebo hyperalgesia. *Journal of Pain Research*, 8, 703–710. <https://doi.org/10.2147/JPR.S91923>
- Aslaksen, P. M., Zwarg, M. L., Eilertsen, H.-I. H., Gorecka, M. M., & Bjørkedal, E. (2015). Opposite effects of the same drug. *Pain*, 156(1), 39–46. <https://doi.org/10.1016/j.pain.0000000000000004>
- Bartels, D. J. P., van Laarhoven, A. I. M., Haverkamp, E. A., Wilder-Smith, O. H., Donders, A. R. T., van Middendorp, H., van de Kerkhof, P. C. M., & Evers, A. W. M. (2014). Role of Conditioning and

Verbal Suggestion in Placebo and Nocebo Effects on Itch. *PLoS ONE*, 9(3), e91727–e91727. <https://doi.org/10.1371/journal.pone.0091727>

Bartels, D. J. P., van Laarhoven, A. I. M., Stroo, M., Hijne, K., Peerdeman, K. J., Donders, A. R. T., van de Kerkhof, P. C. M., & Evers, A. W. M. (2017). Minimizing nocebo effects by conditioning with verbal suggestion: A randomized clinical trial in healthy humans. *PLOS ONE*, 12(9), e0182959–e0182959. <https://doi.org/10.1371/journal.pone.0182959>

Blythe, J., Peerdeman, K., Veldhuijzen, D., van Schothorst, M., Thomaidou, M., Laarhoven, A., & Evers, A. (2021). Nocebo Effects on Cowhage-evoked Itch: A Randomized Controlled Trial of Classical Conditioning and Observational Learning. *Acta Dermato Venereologica*, 101(1), adv00370. <https://doi.org/10.2340/00015555>.

Camerone, E. M., Piedimonte, A., Testa, M., Wiech, K., Vase, L., Zamfira, D. A., Benedetti, F., & Carlino, E. (2021). The Effect of Temporal Information on Placebo Analgesia and Nocebo Hyperalgesia. *Psychosomatic Medicine*, 83(1), 43–50. <https://doi.org/10.1097/PSY.0000000000000882>

Colagiuri, B., Park, J., Barnes, K., Sharpe, L., Boakes, R. A., Colloca, L., & Livesey, E. J. (2021). Pre-Exposure, But Not Overshadowing, Inhibits Nocebo Hyperalgesia. *The Journal of Pain*, 22(7), 864–877. <https://doi.org/10.1016/j.jpain.2021.02.008>

Colagiuri, B., & Quinn, V. F. (2018). Autonomic Arousal as a Mechanism of the Persistence of Nocebo Hyperalgesia. *The Journal of Pain : Official Journal of the American Pain Society*, 19(5), 476–486. <https://doi.org/10.1016/j.jpain.2017.12.006>

Colagiuri, B., Quinn, V. F., & Colloca, L. (2015). Nocebo Hyperalgesia, Partial Reinforcement, and Extinction. *The Journal of Pain*, 16(10), 995–1004. <https://doi.org/10.1016/j.JPAIN.2015.06.012>

Colloca, L., Petrovic, P., Wager, T. D., Ingvar, M., & Benedetti, F. (2010). How the number of learning trials affects placebo and nocebo responses. *Pain*, 151(2), 430–439. <https://doi.org/10.1016/j.pain.2010.08.007>

Colloca, L., Sigaud, M., & Benedetti, F. (2008). The role of learning in nocebo and placebo effects. *Pain*, 136(1), 211–218. <https://doi.org/10.1016/j.pain.2008.02.006>

Corsi, N., & Colloca, L. (2017). Placebo and Nocebo Effects: The Advantage of Measuring Expectations and Psychological Factors. *Frontiers in Psychology*, 8. <https://www.frontiersin.org/article/10.3389/fpsyg.2017.00308>

Egorova, N., Benedetti, F., Gollub, R. L., & Kong, J. (2020). Between placebo and nocebo: Response to control treatment is mediated by amygdala activity and connectivity. *European Journal of Pain (London, England)*, 24(3), 580–592. <https://doi.org/10.1002/ejp.1510>

Feldhaus, M. H., Horing, B., Sprenger, C., & Büchel, C. (2021). Association of nocebo hyperalgesia and basic somatosensory characteristics in a large cohort. *Scientific Reports*, 11(1), 762. <https://doi.org/10.1038/s41598>

Freeman, S., Yu, R., Egorova, N., Chen, X., Kirsch, I., Claggett, B., Kaptchuk, T. J., Gollub, R. L., & Kong, J. (2015). Distinct neural representations of placebo and nocebo effects. *NeuroImage*, 112. <https://doi.org/10.1016/j.neuroimage.2015.03.015>

Geers, A. L., Close, S., Caplandies, F. C., Vogel, C. L., Murray, A. B., Pertiwi, Y., Handley, I. M., & Vase, L. (2019). Testing a positive-affect induction to reduce verbally induced nocebo hyperalgesia in an experimental pain paradigm. *PAIN*, 160(10), 2290–2297. <https://doi.org/10.1097/j.pain.0000000000001618>

Geuter, S., & Büchel, C. (2013). Facilitation of Pain in the Human Spinal Cord by Nocebo Treatment. *Journal of Neuroscience*, 33(34), 13784–13790. <https://doi.org/10.1523/JNEUROSCI.2191-13.2013>

Howe, L. C., Goyer, J. P., & Crum, A. J. (2017). Harnessing the Placebo Effect: Exploring the Influence of Physician Characteristics on Placebo Response. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, 36(11), 1074–1082. <https://doi.org/10.1037/hea0000499>

Kong, J., Gollub, R. L., Polich, G., Kirsch, I., LaViolette, P., Vangel, M., Rosen, B., & Kaptchuk, T. J. (2008). A Functional Magnetic Resonance Imaging Study on the Neural Mechanisms of Hyperalgesic Nocebo Effect. *Journal of Neuroscience*, 28(49), 13354–13362. <https://doi.org/10.1523/JNEUROSCI.2944>

Meeuwis, S. H., van Middendorp, H., Lavrijsen, A. P. M., Veldhuijzen, D. S., & Evers, A. W. M. (2021). Open- and Closed-Label Placebo and Nocebo Suggestions About a Sham Transdermal Patch. *Psychosomatic Medicine*, 83(1), 33–42. <https://doi.org/10.1097/PSY.0000000000000862>

- Meeuwis, S. H., van Middendorp, H., van Laarhoven, A. I. M., Veldhuijzen, D. S., Lavrijsen, A. P. M., & Evers, A. W. M. (2019). Effects of Open- and Closed-Label Nocebo and Placebo Suggestions on Itch and Itch Expectations. *Frontiers in Psychiatry*, 10, 436. <https://doi.org/10.3389/fpsy.2019.00436>
- Nir, R. R., Yarnitsky, D., Honigman, L., & Granot, M. (2012). Cognitive manipulation targeted at decreasing the conditioning pain perception reduces the efficacy of conditioned pain modulation. *Pain*. <https://doi.org/10.1016/j.pain.2011.10.010>
- Pazzaglia, C., Testani, E., Giordano, R., Padua, L., & Valeriani, M. (2016). Expectation to feel more pain disrupts the habituation of laser-pain rating and laser-evoked potential amplitudes. *Neuroscience*, 333, 244–251–244–251. <https://doi.org/10.1016/j.neuroscience.2016.07.027>
- Skvortsova, A., Veldhuijzen, D. S., van Middendorp, H., Colloca, L., & Evers, A. W. M. (2019). Effects of Oxytocin on Placebo and Nocebo Effects in a Pain Conditioning Paradigm: A Randomized Controlled Trial. *The Journal of Pain*, 21(3–4), 430–439. <https://doi.org/10.1016/j.jpain.2019.08.010>
- Thomaïdou, M. A., Blythe, J. S., Houtman, S. J., Veldhuijzen, D. S., van Laarhoven, A. I. M., & Evers, A. W. M. (2021). Temporal structure of brain oscillations predicts learned nocebo responses to pain. *Scientific Reports*, 11(1), 9807. <https://doi.org/10.1038/s41598-021-89368-0>
- Thomaïdou, M. A., Veldhuijzen, D. S., Meulders, A., & Evers, A. W. M. (2021). An experimental investigation into the mediating role of pain-related fear in boosting nocebo hyperalgesia. *Pain*, 162(1), 287–299. <https://doi.org/10.1097/j.pain.0000000000002017>
- Thomaïdou, M. A., Veldhuijzen, D. S., Peerdeman, K. J., Wiebing, N. Z. S., Blythe, J. S., & Evers, A. W. M. (2020). Learning mechanisms in nocebo hyperalgesia: The role of conditioning and extinction processes. *Pain*, 161(7), 1597–1608. <https://doi.org/10.1097/j.pain.0000000000001861>
- Tinnermann, A., Geuter, S., Sprenger, C., Finsterbusch, J., & Büchel, C. (2017). Interactions between brain and spinal cord mediate value effects in nocebo hyperalgesia. *Science*, 358, 105–108.
- Tu, Y., Wilson, G., Camprodon, J., Dougherty, D. D., Vangel, M., Benedetti, F., Kaptchuk, T. J., Gollub, R. L., & Kong, J. (2021). Manipulating placebo analgesia and nocebo hyperalgesia by changing brain excitability. *Proceedings of the National Academy of Sciences*, 118(19), e2101273118. <https://doi.org/10.1073/pnas.2101273118>
- van de Sand, M. F., Menz, M. M., Sprenger, C., & Büchel, C. (2018). Nocebo-induced modulation of cerebral itch processing – An fMRI study. *NeuroImage*, 166, 209–218. <https://doi.org/10.1016/j.NEUROIMAGE.2017.10.056>
- van den Broeke, E. N., Geene, N., van Rijn, C. M., Wilder-Smith, O. H. G., & Oosterman, J. (2014). Negative expectations facilitate mechanical hyperalgesia after high-frequency electrical stimulation of human skin: Negative expectations and mechanical hyperalgesia. *European Journal of Pain*, 18(1), 86–91. <https://doi.org/10.1002/j.1532-2149.2013.00342.x>
- Van Laarhoven, A. I. M., Vogelaar, M. L., Wilder-Smith, O. H., Van Riel, P. L., Van De Kerkhof, P. C., Kraaijmaat, F. W., Evers, A. W. M. (2011). Induction of nocebo and placebo effects on itch and pain by verbal suggestions. *Pain*, 152(7), 1486–1494. <https://doi.org/10.1016/j.pain.2011.01.043>
- Vögtle, E., Barke, A., & Kröner-Herwig, B. (2013). Nocebo hyperalgesia induced by social observational learning. *Pain*, 154(8), 1427–1433. <https://doi.org/10.1016/j.pain.2013.04.041>
- Weï, H., Zhou, L., Zhang, H., Chen, J., Lu, X., & Hu, L. (2018). The Influence of Expectation on Nondeceptive Placebo and Nocebo Effects. *Pain Research and Management*, 2018, 1–8. <https://doi.org/10.1155/2018/8459429>
- Weng, L., Peerdeman, K., Della Porta, D., Laarhoven, A. I. M., & Evers, A. (2021). Can placebo and nocebo effects generalize within pain modalities and across somatosensory sensations? *Pain*, Publish Ahead of Print. <https://doi.org/10.1097/j.pain.0000000000002390>

