Placebo and nocebo effects in itch : from conditioning to psychophysiological effects

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Chapter 2

Placebo and nocebo effects across itch and dermatological conditions: a systematic review

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ABSTRACT

Placebo and nocebo effects have a large influence on somatic symptoms such as pain. For itch and other dermatological symptoms these effects have been far less investigated. The current review systematically integrates for the first time evidence from both animal (mainly rodents, but also non-human primates) and human trials on the elicitation of placebo and nocebo responses in itch, itch-related symptoms and conditions of the skin and mucous membranes, and related immune outcomes (e.g., histamine). Thirty-one animal studies, twenty-one human studies with healthy participants, and thirty-four human studies with patients were included. Overall, studies consistently show that placebo and nocebo effects can be induced by various methods (e.g., suggestions, conditioning and social cues), despite a high level of heterogeneity across studies. Effects of verbal suggestions were found consistently across subjective (e.g., itch in humans) and behavioral (e.g., scratching in animals) parameters, whereas conditioning was likely to impact physiological parameters under certain conditions (e.g., more pronounced conditioning of histamine levels in stressed rodents). Brain areas responsible for processing of itch were associated with nocebo effects in itch. Future research should investigate how variations in methods may impact placebo and nocebo effects, and whether all symptoms and conditions can be influenced equally.

INTRODUCTION

Placebo and nocebo effects are known to influence symptom severity and treatment efficacy in various medical symptoms and conditions [1-4]. Placebo effects can be described as beneficial effects that are not due to a (pharmacologically) active treatment component, but are rather elicited by contextual cues, or by positive expectations regarding treatment outcomes [5,6]. Nocebo effects are adverse treatment outcomes (e.g., increased side effects, reduced treatment efficacy) elicited by non-active treatment components [5]. Studies show that placebo and nocebo effects can be experimentally induced by, among other things, conditioning (associative learning), expectancy manipulations through providing positive or negative information (verbal suggestions) about treatment outcomes (instructional learning), or by social cues (e.g., learning by observing others) [6-8]. In addition, some work suggests that placebo effects may still occur when it is known that a placebo is given (open-label placebo) [9-13].

Placebo and nocebo effects have been found to impact various somatic symptoms such as pain and itch [3]. Itch is a key symptom of many dermatological conditions [14,15], has a high impact on patients' quality of life and has high economic costs [16-18]. The estimated lifetime prevalence of itch in the general population is 7-22%, and in patients with a skin disease estimates are set on 100% [19]. Most often, itch is evoked in the skin by mediators (e.g., histamine) eliciting changes in the chemical environment that are detected by C nociceptive fibers (capable of transmitting noxious stimuli, including itch and pain) to regions in the brain stem, the thalamus, somatosensory cortex, as well as areas involving emotion and reward [20]. A meta-analysis shows that at least 30 percent of itch reduction in randomized controlled trials can be explained by placebo effects [21]. Research shows that such placebo effects may occur through top-down processes stemming from brain regions involved in planning, emotion regulation, as well as brain regions specific to the symptom or condition for which they occur, and that they can moreover be evoked by expectations regarding treatment outcomes [22,23].

Most studies demonstrate that placebo and nocebo effects can be induced by verbal suggestions, for example, for self-reported symptoms of itch. There is some evidence, however, that these effects can also be elicited for physiological parameters related to itch, for instance, for wheal or flare responses to histamine [24]. Literature moreover shows that conditioning can influence immune parameters in animal models and human populations [25-27]. As such, conditioning may potentially be used to influence the immune pathways

underlying itch and cutaneous conditions as well. Although narrative reviews emphasize the impact of placebo and nocebo effects on itch [3,7,8], a systematic overview of studies investigating placebo and nocebo effects, which also encompasses the immunomodulatory aspects of these effects, has not been provided yet. Providing such an overview could provide new insights in the consistency of placebo and nocebo effects found across induction methods, clinical conditions, and symptoms. The current review therefore aims to summarize the available knowledge of placebo and nocebo effects that were experimentally elicited in controlled trials in cutaneous conditions, in symptoms of the skin or atopic symptoms of the mucous membranes that are associated with itch, as well as in related experimental human (i.e. healthy participants) or animal models.

RESULTS

Search results and study characteristics

An overview of the literature search and number of articles in each step of the selection procedure can be found in **Figure 1**. In total, the literature search identified 16.440 unique studies, of which 79 were considered eligible for inclusion. An additional 7 studies were identified by screening the reference lists of the included studies, bringing the total to 86 articles that were included in this review (k=31 animal and k=55 human studies). Articles that were identified through reference lists did not have keywords listed online, or provided no online abstract and were therefore not found in the systematic search. A semi-quantitative overview of effects for each induction method and outcome type is provided in **Table 1** (with a graphical representation and short summary being given in **Supplementary Figure S1 and Supplementary Table S1,** respectively). An extensive overview of the study characteristics and a short summary of results is presented for animal and human studies separately (with human studies further split into healthy volunteers and patient studies) in **Supplementary Tables S2, S3 and S4**.

Risk of bias assessment

An overview of the risk of bias assessment outcomes is provided separately for animal and human studies, in **Supplementary Figures S2-S5**. The quality of the 86 included studies varied. None of the included animal studies met all criteria for risk of bias, most often due to a lack of important information to decide risk of bias. For human studies, more information was provided, and risk of bias was lower. In general, no differences in risk of bias were detected between studies that reported null findings and studies that reported significant findings. Studies on verbal suggestions combined with hypnosis more often had a selection bias compared to the other studies – participants who were highly hypnotizable were often selected, which may have increased bias in the study findings. In addition, some studies on verbal suggestions had high risk of bias for blinding, mostly due to the personnel that assessed outcomes not being blinded to allocated groups.

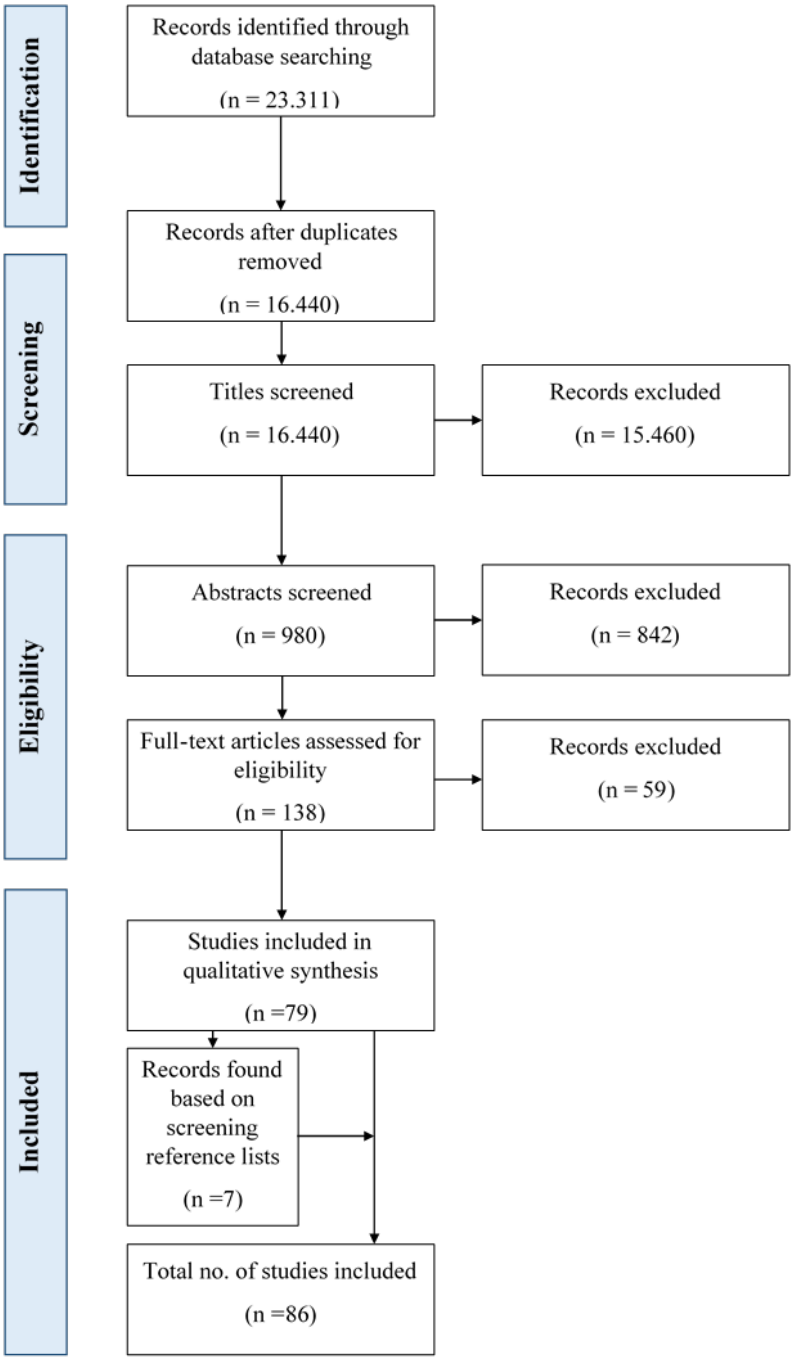

Figure 1. Flowchart for the selection of articles to be included in the systematic review.

Table 1. Semi-quantitative overview of outcomes for each study, separated for animal studies, and human studies subdivided in healthy participant and patient samples.

Sample type	Type of induction	Mechanism(s)	Outcome category	Outcome classification	
				Confirmation of hypothesis*	**Non-confirmation of hypothesis**
Animal	**Placebo**	Conditioned immunosuppression	Behavioral	Saccharin preference ratio [28,30,115-118]	-
			Physiological	DTH response to SRBC: hemagglutination titers [115,117,118], paw swelling [29], footpad swelling [30], plasma glucocorticoids [30], DNCB-induced ear swelling [116], left/right ear weight ratio [119], leukocyte migration inhibitory factor [119] Sensitization to corticosterone: DTH-induced paw swelling [28]	-
	Nocebo	Conditioned allergic responses and anaphylactic shock	Behavioral	Saccharin preference ratio [120-122], Anaphylactic shock behavior [120,121], breathing pattern indicative of asthmatic attack [32], asthma attack [123], lung anaphylactic response [33]	Breathing pattern indicative of asthmatic attack [31], rearing behavior [33], freely acting plus maze behavior [33]
			Physiological	Plasma histamine levels [34-39,124,125], lung tissue histamine levels [34], rat mast cell protease II [126], plasma cortisol levels [37], plethysmographic amplitude [127], corticosterone levels [33]	Plasma histamine levels [34], bronchoalveolar lavage fluid [34], respiratory resistance [35]
		Operant conditioning	Behavioral	Scratching behavior [41]	Scratching behavior [40]
		Social induction	Behavioral	Scratching behavior [42-44], attention (looking behavior) [45]	Scratching behavior [45], attention (looking behavior) [43]
Sample type	**Type of induction**	**Mechanism(s)**	**Outcome category**	**Outcome classification**	
				Confirmation of hypothesis*	**Non-confirmation of hypothesis**
Healthy participants	**Placebo**	Verbal suggestions + hypnosis	Self-reported	Laser-induced and histaminergic pain [46]	
			Physiological	Wheal area (Prausnitz-Küstner reaction to horse serum) [47], wheal area to histamine [48], titration gradients [48], histaminergic flare [46,51], Mantoux skin response [51]	Titration endpoint data [48], wheal/erythema ratio [49,50], histamine wheal [51], erythema [52], skin thickness [52]

Table 1. *continued (2 of 3).*

Sample type	Type of induction	Mechanism(s)	Outcome category	Outcome classification	
				Confirmation of hypothesis*	**Non-confirmation of hypothesis**
		Verbal suggestions	Self-reported	Expected wheal area [53], self-rated itch in response to histamine [54], expected itch [55,56], expected pain [55,56], expected fatigue [55], self-rated pain during CPT [56], mechanically induced itch [58], electrically induced itch [58], chemically induced itch (histamine) [58], mechanically induced pain [58], electrically induced pain [58], chemically induced pain (histamine) [58]	**Itch + anxiety levels [57] not described** Self-rated itch [55,56], self-rated pain [55], self-rated fatigue [55], physical sensitivity [55], chemically induced itch (histamine) [58]
			Physiological	Heart rate [53], histamine wheal area [57], histaminergic flare [57]	Histamine wheal area [53,54,56], heart rate variability [53], heart rate [55], skin conductance [55], skin temperature [56]
		Verbal suggestions (OL)	Self-reported	Expected itch [59]	Self-rated itch in response to histamine [59], self-reported skin response [59]
			Physiological	-	Wheal area [59], flare area [59]
		Conditioning (+ VS)	Self-reported	Electrically induced itch [60]	-
	Nocebo	Verbal suggestions	Self-reported	Self-rated itch [24], self-rated unpleasantness [24]	-
			Physiological	Wheal intensity (NaCl) [24], histaminergic flare intensity [24]	-
		Conditioning (+ VS)	Self-reported	Self-rated itch [61,62]	-
			Physiological	fMRI: activity in contralateral rolandic operculum [62], functional coupling between periaqueductal gray [62]	-
		Social induction	Self-reported	Self-rated itch [63-65]	-
			Behavioral	Scratching [63-65]	-
				fMRI: activation of major areas of itch matrix (thalamus, primary somatosensory cortex, premotor cortex, insula) [63]	-

Sample type	Type of induction	Mechanism(s)	Outcome category	Outcome classification	
				Confirmation of hypothesis*	**Non-confirmation of hypothesis**
Patients	**Placebo**	Verbal suggestions + hypnosis	Self-reported	Cutaneous pain threshold [66], atopic eczema symptoms [66], retrospectively assessed symptoms of allergy [67], nasal flow symptoms during challenge (NPT) [67], self-rated itch [68]	Daily self-report symptoms of allergy [67], nasal flow symptoms after challenge (NPT) [67]

Table 1. *continued (3 of 3).*

Sample type	Type of induction	Mechanism(s)	Outcome category	Outcome classification	
				Confirmation of hypothesis*	**Non-confirmation of hypothesis**
			Physiological	Skin temperature [69], skinfold thickness [69], allergen-induced wheal size [70], allergen induced flare size [70], histaminergic flare size [128], number of warts**** [71,72,74]	Allergen-induced wheal size [70], allergen induced flare size [70], histamine wheal size [128,129], histaminergic flare [129], phosphate dilutions [129], number of urticaria wheals [68], clinical psoriasis severity [73], delayed blanch of skin [130], histaminergic flare [130], white line response [130]
		Verbal suggestions (OL, +inert pill)	Self-reported	Allergic symptoms composite score [75,76]	Allergic symptoms: separate scores [75]
		Pharmacological conditioning / conditioned dose reduction	Self-reported	Psoriasis severity scale [79]	Allergic symptoms [77], Allergic symptoms in response to NPT [78]
			Physiological	Psoriasis relapse [79], basophil activation [77]	Wheal size in response to allergens [77,78], blood count & flow cytometry [77]
		Conditioning (+ VS)	Self-reported	Pain in response to electrical stimulation [80]	-
		Social induction	Physiological	Wheal size in response to histamine [81]	-
	Nocebo	Verbal suggestions + hypnosis	Physiological	Skin temperature [82]	-
		Verbal suggestions	Self-reported	Self-rated itch [83]	-
			Physiological	Conductance – thoracic gas volume ratio [85,86], airway resistance [85,86] fMRI: increase in dorsolateral prefrontal cortex, caudate, and intraparietal sulcus [83]	Wright-McKerrow Peak Flow Meter outcomes [84], maximum expiratory flow rate [84], respiratory pattern [84]
		Conditioning [A]	Self-reported		Subjective allergic symptoms [87,88]
			Physiological	Peak nasal inspiratory flow [87], blood serum histamine levels [87], nasal tryptase levels [88]	Wheal size in response to sham allergen [89]
		Social induction	Self-reported	Self-rated itch [92-95]	Self-rated itch (HC only) [93]
			Behavioral	Scratching behavior [92-95], allergic symptoms [96]	-
			Physiological	Breathing frequency [96] fMRI: higher activity in SMA, the left ventral stratium and higher right OFC activation [95]	Airflow [96], tidal volume [96], inspiratory time [96], respiratory resistance [96]

Note (table 1). * A confirmation of hypothesis is defined as a significant ($p<.05$) difference of the experimental group(s) with a) included control groups or b) a baseline measurement, that indicates successful placebo or nocebo induction in line with the proposed hypothesis (e.g., increased paw swelling following conditioning of a CS with antigens [animals], or itch reduction following suggestions of lower itch, or itch exacerbation following suggestions of an increase in itch [humans]). This included studies for which effects were conditional (e.g., depending on stress or isolation [animals], effects depending on depth of hypnosis [humans]). ** A non-confirmation of hypothesis is defined as either a non-significant ($p>.05$) difference of the experimental group(s) with a) included control groups or b) a baseline measurement, or a significant in the opposite direction of the proposed hypothesis.

CPT = cold pressor task, HC = healthy controls, OL= open-label, NPT = nasal provocation test, VS = verbal suggestions.

[A] Two out of five studies (Jordan, 1972, and Robertson, 1975) compared the efficacy of conditioning scratch responses for patients and healthy controls. While it was concluded that scratch responses were more easily conditioned in patients, no remarks regarding the efficacy of conditioning itself were made (i.e. no comparisons with control groups / a non-conditioned state). As such, these were not counted amongst the proportional positive results (confirmed hypotheses) in the table.

Animal studies

Of all thirty-one animal studies, most investigated effects in rodents (guinea pigs k=12; rats k=11; mice k=4; both rat and mice k=1) or non-human primates (k=3; exclusively included in studies on social induction of scratching behavior). The number of animals included in each experiment ranged from 5 to 96. Three studies did not report sample size. Most (k=18; 58%) included male samples exclusively, followed by studies that included both sexes (k=5; 16%) or females exclusively (k=4; 13%). A minority (k=4; 13%) did not report the sex of the animals. Most animal studies were conducted before 1990 (k=19; 61%), and only a few took place within the last 10 years (2010-2019: k=3; 10%).

1. Placebo effects

1.1. Conditioned immunosuppression

Eight studies investigated whether allergic responses could be suppressed by conditioning of a neutral stimulus (or conditioned stimulus, CS; e.g., a saccharin solution or an odor) with a pharmacological drug (unconditioned stimulus; UCS) in rodent models of delayed-type hypersensitivity responses. Saccharin preference ratio (i.e. behavioral parameter – the amount of saccharin that was ingested by the animal in a subsequent testing phase following conditioning) was reduced in all studies (k=6) that assessed this parameter. Evidence of conditioned immunosuppression was found for most physiological parameters (i.e., for hemagglutination titers, ear or paw swelling, and leukocyte migration to the area of antigen injection). Conditioning did not affect paw swelling when dexamethasone was used as UCS [28]. One study found extinction of conditioned responses following the first of three re-exposures [29]. Moreover, one study indicated that conditioned effects are dependent on the induction of stress [30], suggesting that conditioned responses may be context-specific.

2. Nocebo effects

2.1. Conditioned allergic responses and anaphylactic shock

Twelve studies investigated whether an allergic response could be learned through conditioning in rodent models by pairing a cue (the CS, for example, an odor) with an

allergen or substance for which animals were previously sensitized. Behavioral parameters were influenced in 5 of the 7 studies that assessed them: saccharin preference ratio decreased following conditioning in all studies (k=3), whereas behavior indicating anaphylactic shock or asthmatic attack increased in 2 of 4 studies. In the two studies that overall reported null effects, behavior indicating an asthmatic attack remained unchanged in one study [31], while another found conditional effects: exposure to the CS led towards asthmatic attacks – but only when animals were stressed [32]. It was demonstrated that freely-acting behavior (e.g., rearing, locomotion) did not change following conditioning [33]. Changes in physiological parameters were found following conditioning, which were indicative of an allergic response (i.e., increases in histamine serum levels, Rat Mast Cell Protease II, or lung tissue histamine levels; increased plethysmographic amplitude, and respiratory resistance, see also **Table 1)**. Two studies failed to find effects on (secondary) physiological outcomes [34,35]. Others showed mixed evidence for conditioned histamine release in rodents: it was shown that effects depended on handling-induced stress [36,37], fasting stress [35], anesthetization [34], or receiving medication such as diazepam [38] or dexamethasone [39]. For example, conditioned histamine release occurred exclusively in stressed animals.

2.2. (Operant) Conditioning of scratch responses

Two studies described a series of experiments, in which it was investigated whether scratching behavior could be operationally conditioned by reinforcing bouts of scratching with food [40,41]. One study found scratching to be less readily conditioned compared to rearing or washing [40], while the other found that scratching could be increased through operant conditioning – with the behavior being more easily conditioned when an itchy stimulus (i.e. collar) was present [41].

2.3. Social induction

Four studies investigated whether scratching behavior could be contagious in animals (k=1 in rodents, k=3 in non-human primates). The most common designs consisted of either observing a live same-species animal, or of observing videos in which scratching behavior was displayed. Two studies found that scratching behavior in observers (i.e., animals that watched others scratching) increased [42,43], while two other studies found that scratching did not increase following observation of another animal scratching [44,45].

Healthy volunteers

Of the 21 studies with healthy volunteers, most studies included both males and females (k=16; 77%). Two studies (9%) were stratified by sex (50:50 distribution in experimental groups) or investigated females exclusively (k=3; 14%). Sample sizes ranged between 10 to 159 healthy volunteers. Most studies were conducted in the past 10 years (2010-2019: k=13, 64%).

1. Placebo effects

In total, fourteen studies were included that investigated placebo effects by verbal suggestions. A single study investigated the induction of placebo effects by conditioning combined with verbal suggestions (described in subsection '2.4.1.2. Conditioning').

1.1. Verbal suggestions

Across studies, a further subdivision could be made for studies that induced placebo effects by: a combination of verbal suggestions and hypnosis (k=7), by verbal suggestions exclusively (k=6), or by open-label verbal suggestions (k=1). Three of the seven studies that provided positive verbal suggestions with hypnosis demonstrated improvement in self-reported (i.e., pain induced by laser and histamine skin prick tests, [46]) and physiological parameters (i.e., skin responses to histamine and horse serum such as wheal and flare, titration gradient and endpoints, pain-related brain potentials) [46-48]. One study found that effects on wheal area were a function of the depth of the trance induced by hypnosis [47]. In addition, four studies compared suggestions of decreased responses to antigens or histamine for one arm with suggestions of increased responses for the other arm within subjects. All four studies included or divided participants on being highly hypnotizable [49-52]. Only one study reported significant differences in skin thickness following suggestions at certain dilution strengths of the test substance [51]. The others reported no effects. Four studies investigated placebo effect induction by positive verbal suggestions exclusively. Expected itch, pain or skin responses were reduced following positive suggestions in all studies [53-56]. Three studies assessed histamine-induced itch [54-56], but only one of these found lower itch following suggestions [54]. Positive suggestions reduced pain during a cold-pressor task in one study [56], but not in another [55]. Wheal area was not affected by suggestions in any study. Two studies compared positive suggestions with negative suggestions [57,58]: overall, findings were mixed. In one study, suggestions of high and

low itch or pain were able to respectively enhance and decrease self-reported parameters of itch and pain after mechanical and electrical stimulation, but suggestions of low itch did not reduce histamine-induced itch [58]. In another study, physiological parameters (i.e. flare, wheal) differed between positive and negative suggestions groups, but no differences were found compared to a neutral control group [57]. Finally, a single study investigated whether open-label positive verbal suggestions could induce positive expectations and placebo effects for itch compared to a neutral control [59]. Suggestions decreased itch expectations, but not itch. No effects on physical skin response (histaminergic flare (area), skin temperature, wheal area) were found.

1.2. Conditioning

A single study investigated placebo effect induction by conditioning, verbal suggestions, and by combining suggestions and conditioning. While no significant reduction in electrically induced itch was found following conditioning exclusively or following verbal suggestions exclusively, a combination of the two did result in reduced itch levels [60].

2. Nocebo effects

In total, seven studies investigated nocebo effects in healthy volunteers. Nocebo effects were induced by verbal suggestions (k=1), conditioning (k=1), a combination of verbal suggestions and conditioning (k=2; described in the subsection '2.4.2.2. conditioning'[1]), or by social cues (k=3; contagious itch).

2.1. Verbal suggestions

In the study that focused exclusively on suggestions-induced nocebo, participants received information (verbal suggestions) about the severity to which they would respond to histamine and saline skin prick tests [24]. Itch, unpleasantness of the test, and wheal diameter were higher in response to saline, and the histaminergic flare (measured by diameter) was greater following negative suggestions [24].

[1] This includes the study of Bartels et al. (2014) that is also described under subsection '2.4.1. placebo effects', as both placebo and nocebo effects were investigated within this study.

2.2. Conditioning

Three studies investigated nocebo effect induction by conditioning. One study demonstrated successful nocebo effect induction by conditioning for itch. Moreover, the study showed that these learned responses could be reversed by positive suggestions, and demonstrated generalization of effects from electrical to histamine-induced itch [61]. Two studies found that conditioning and verbal suggestions could both increase itch [60,62]. In addition, one of these reported that a combination was most effective to induce nocebo effects [60]. Using functional magnetic resonance imaging (fMRI), increased activity was found in the contralateral Rolandic operculum, and increased functional coupling was found between the insula and the periaqueductal gray (PAG), all areas involved in the somatosensory processing of histaminergic itch [62].

2.3. Social induction

Three studies investigated whether itch could be induced by social or contextual factors in healthy participants, using a variety of methods to induce itch sensations: videos of people scratching [63], slideshows of itch-related pictures [64], or itch suggestions during music, which were presented either sub- or supra-liminally [65]. Itch and scratching behavior were increased in 2 of 3 studies [63,64]. In the remaining study, findings were mixed: itch and scratching were increased only when suggestions were presented supra-liminally during music, but not when presented super-liminally [65]. Watching itch-inducing videos moreover activated major areas of the itch matrix (thalamus, primary somatosensory cortex, premotor cortex (BA6), and insula) as demonstrated through fMRI [63].

Patients

In the 34 studies on placebo and nocebo effects within patient samples, the investigated medical conditions were: allergic rhinitis (including, but not limited to, hay fever and dust mite allergy) (k=10; 29%), atopic dermatitis (k=9; 26%), allergic asthma (or other lung problems associated with irritation by allergens, e.g., bronchitis) (k=6; 18%), warts (k=3; 9%), psoriasis (k=2; 6%), chronic urticaria (k=1; 3%), lichen simplex (k=1; 3%), multiple conditions combined (k=1; 3%), or unspecified skin diseases (k=1; 3%). Most studies included both male and female patients (k=23; 67%), but some did not describe sample sex (k=11; 33%). The majority of studies took place either within the last ten years (2010-2019: k=9, 27%) or before 1970 (k=8, 24%).

1. Placebo effects

In total, nineteen studies investigated placebo effects in patient samples. Placebo effects were elicited by positive verbal suggestions and hypnosis (k=12), by open-label suggestions (k=2), by conditioning (k=4) or by social induction (k=1).

1.1. Verbal suggestions

Across studies investigating placebo effect induction by suggestions, medical conditions investigated were: allergy (k=4), warts (k=3), allergic asthma (k=2), atopic dermatitis (k=2), chronic urticaria (k=1), psoriasis (k=1), and multiple conditions combined (k=1). In the twelve studies on suggestions and hypnosis, eleven provided suggestions of non-responding (e.g., to allergens) or symptom relief. Four studies investigated self-reported symptoms, with three demonstrating significant induction of placebo effects (in one of these studies, effects were found exclusively when symptoms were assessed retrospectively) [66-68]. Physiological parameters (e.g., clinical symptoms of skin conditions, such as wheals or warts) were assessed in 10 studies, and were generally reduced following suggestions and hypnosis in 3 studies [69-71]. In the other 7 studies, no or mixed evidence was found. One study gave suggestions of improvement for one side of the body and concluded that any observed improvement was on that side, however, no data or statistical tests were reported [72]. Some studies noted that symptoms improved only when deep hypnosis was achieved [73,74]. Finally, two studies investigated whether open-label placebo effects could be induced for allergic rhinitis [75,76]. A briefing about the placebo effect was given together with inert pills (in addition to treatment as usual) in one study [75]. In the other, both separate and combined effects of the briefing and the inert pills were examined [76]. Open-label placebo effects were induced for allergic symptoms in both studies. Moreover, while the inert pills reduced allergic symptoms, no additional effect of the open-label briefing was found [76].

1.2. Conditioning

Medical conditions investigated were allergy (k=2), psoriasis (k=1), and atopic dermatitis (k=1). Studies on conditioning placebo effects in patient samples could be further subdivided into pharmacological conditioning (k=2), conditioned dose reduction (k=1), or suggestions and conditioning (k=1). In the two studies on placebo effects by pharmacological (antihistamine) conditioning for allergic rhinitis, no effects on subjective symptoms or wheal size were found [77,78]. Basophil activation after exposure to allergens

was reduced, however, which is indicative of conditioned immunosuppression [77]. In the single study that investigated conditioned dose reduction (i.e., using conditioning principles to partially replace medication by placebo), findings were mixed: although conditioned dose reduction prevented psoriasis relapse overall, significant improvement in symptoms was demonstrated only in one of two research sites [79]. Finally, a single study investigated whether verbal suggestions, conditioning, or a combination of both could influence electrically-induced pain in atopic dermatitis and healthy controls [80]. Verbal suggestions, but not conditioning, reduced pain in both atopic dermatitis and healthy controls. Moreover, a combination of suggestions and conditioning was most effective.

1.3. Social induction

A single study assessed whether advertising of antihistamine brands would influence drug efficacy (defined as % decrease in wheal) in allergic vs. non-allergic participants [81]. Two types of advertisements were shown, one where only brand A (the antihistamine used in the study) was promoted, and one where brand B was promoted as working faster than A. Decreased efficacy was found for allergic participants at 60 minutes following antihistamine use when brand A was promoted, compared to when brand B was promoted. For non-allergic participants, increased efficacy was found when brand A was promoted at 120 minutes following antihistamine use.

2. Nocebo effects

In total, fifteen studies investigated nocebo effects in patient samples. Nocebo effects were elicited by negative verbal suggestions (k=5), by conditioning (k=5), or by social induction (k=5).

2.1. Verbal suggestions

Across studies investigating nocebo effect induction by suggestions, medical conditions examined were: atopic dermatitis (k=2), allergic asthma (k=2), and other lung problems related to irritants or allergens (k=1). One study investigated negative verbal suggestions with hypnosis, and four investigated negative verbal suggestions exclusively. Following suggestions and hypnosis, higher skin temperature was found in both atopic dermatitis and healthy controls [82]. Another study in atopic dermatitis investigated nocebo effects induction by suggestions exclusively, and found that this increased self-reported itch [83].

Moreover, fMRI signal increased following suggestions in the dorsolateral prefrontal cortex, caudate, and intraparietal sulcus – all regions involved in motivational and cognitive processing, and all regions that respond when real allergens are presented [83]. Finally, three studies investigated effects of negative suggestions on physiological parameters representing airway reactivity [84-86]. One study failed to find effects of negative suggestions on physiological parameters (i.e., respiratory pattern, maximum expiratory flow) in bronchial asthma [84]. In the other two studies, suggestions did elicit significant changes in physiological parameters (i.e., airway resistance, thoratic gas volume, conductance-thoratic gas volume ratio) indicative of bronchoconstriction [85,86]. Moreover, positive suggestions (i.e., that a bronchodilator was given) reversed these effects [86].

2.2. Conditioning

Five studies investigated whether nocebo effects could be induced by conditioning in allergic rhinitis (k=3), atopic dermatitis (k=1), and lichen simplex (k=1). No effects of conditioning on self-reported allergic symptoms were found [87,88]. Physiological parameters (i.e., peak nasal inspiratory flow, histamine level, nasal tryptase level) increased following conditioning in 2 studies [87,88], while another failed to find effects (i.e., for wheal response to sham allergens) [89]. Generally, conditioned effects were stronger when the number of acquisition trials increased, and effects were prone to extinction [87]. Finally, for patients with atopic dermatitis and lichen simplex, conditioning led to a higher number of scratch responses compared to healthy controls [90,91].

2.3. Social induction

Five studies investigated whether symptoms such as itch could be induced socially (e.g., contagious itch, induced by a lecture on itch, scratching videos, or pictures of allergens) in atopic dermatitis (k=3), non-specified skin diseases (k=1) or allergic asthma (k=1). Three studies compared patients with healthy controls. Self-reported parameters (i.e. itch, asthma symptoms composite score) and scratching behavior were increased following social induction in all studies that measured these outcomes. Both self-reported and behavioral parameters increased more for patients compared to healthy controls [92-95]. Moreover, fMRI data showed that activation of the supplementary motor area, the left ventral striatum and the right orbitofrontal cortex increased following an itch video compared to a control video – all regions that are particularly associated with the desire to scratch in itch [95].

While breathing frequency increased in response to allergen pictures in allergic asthma, no changes were detected for other (physiological) respiratory parameters [96].

DISCUSSION

This review summarizes the available knowledge on experimentally induced placebo and nocebo effects in cutaneous conditions, and symptoms of the skin or atopic symptoms of the mucous membranes associated with itch, in relevant animal or human models (i.e., healthy participants and patients). In general, considerable evidence is provided for placebo and nocebo effects in medical conditions and symptoms relevant to the field of dermatology. Placebo and nocebo effects were elicited in self-reported and behavioral parameters related to symptoms (e.g., itch, allergic symptoms or other self-reported symptoms, scratching behavior). Effects could also be induced for physiological parameters, most notably when (pharmacological) conditioning or a combination of suggestions and conditioning were used. Generally, findings were less consistent for physiological parameters than for self-reported or behavioral parameters. The findings illustrate that placebo and nocebo effects can be induced through similar mechanisms across animal studies, studies using healthy volunteers, and studies with patients, despite a high level of heterogeneity across studies.

Animal studies show that both placebo and nocebo effects may be elicited through associative learning (conditioning). It was demonstrated that allergic reactions can be conditioned, which is indicative of a nocebo effect. Likewise, placebo effects were shown in rodent models of allergy (i.e. modelled hypersensitivity responses), as demonstrated by studies investigating conditioned immunosuppression. However, the methods used within these studies were very diverse. For example, the way in which hypersensitivity is modeled in rodents differed, as did the conditioning paradigms used: both CS and UCS were heterogeneous amongst studies, the number of acquisition and evocation sessions varied, and the specific control groups differed between studies (see **Supplementary Table S2**). There was consistency in behavioral outcomes, but physiological outcome parameters varied depending on the specific sensitization method and unconditioned stimulus that were used. Overall, the studies illustrate that learned placebo effects are moreover sensitive to the context (they may not be elicited when the context changes) and are prone to extinction [29,30,34-39]. In the future, research may consider systematically investigating which

conditioning paradigms are most effective. Moreover, replication and generalization of the conditioning paradigms used in previous studies may be considered.

Of all human studies included in the review, the outcome parameters used were most consistent in studies with healthy participants – with self-reported measures of itch and physiological outcomes of wheal and flare responses to histamine being most often assessed [97,98]. Most models with healthy participants simulate cutaneous conditions by mechanical, electrical, and chemical (i.e., histamine) stimulation of the skin. Effects were found most consistently for self-reported outcomes such as itch, and behavioral outcomes such as scratching. Physiological outcomes, on the other hand, were less consistently influenced. In patient samples, similar trends in study outcomes were observed, with self-reported and scratching behavior generally more likely to be affected than physiological parameters. Most studies investigated – and found placebo and nocebo effects for – atopic dermatitis and allergic rhinitis, with only a small body of research done on placebo and nocebo effects in other conditions (e.g., psoriasis, chronic urticaria, and other skin diseases). Future research may consider replicating these findings, as well as extending them to other dermatological conditions, in order to assess similarity of effect sizes for different symptom etiologies. It should be noted that the manner of placebo and nocebo effect induction varied a lot across human trials (both for healthy participants and patients). Overall, different mechanisms (i.e., verbal suggestions, conditioning, social induction) were used to elicit placebo and nocebo effects – furthermore, even in case of similar mechanisms, other variances in the study design (e.g., type of instructions, dissimilarities in conditioning paradigm) may complicate the comparability of placebo and nocebo effect sizes across studies. In trials with patients, an additional confounding factor is added by heterogeneity across medical conditions and condition-dependent outcome parameters.

Finally, few studies have investigated neurological pathways and brain areas that are involved in placebo and nocebo effects for dermatological symptoms such as itch. Placebo and nocebo effects may modulate itch through top-down processing in brain areas related to the specific condition or symptom in which they emerge [23]. Indeed, work on itch shows that brain areas likely involved in nocebo responding are those that are responsible for somatosensory processing of itch or are otherwise related to the itch-scratch cycle as well [62,63,83,95]. Caution is needed in interpreting these findings, however, as only nocebo effects have been investigated. Moreover, of the four studies on brain processing of nocebo effects in itch, two were investigating contagious itch. Mirror neurons (i.e., activated when mirroring facial expressions for affective or empathetic purposes) have been proposed to

play a role in eliciting contagious itch [99]. It unclear whether or how this may relate to nocebo effects induced by other means. In addition, brain processing of placebo effects in itch have not yet been investigated. Future research may aim to further identify brain regions of interest for both placebo and nocebo effects processing.

It has been proposed previously that verbal suggestions are more likely to elicit effects on self-reported outcomes in humans – either alone, or in combination with conditioning [3,8,98], whereas for physiological outcome parameters, (pharmacological) conditioning may be more likely to elicit effects. The studies included in the current review likewise underline this notion. Moreover, findings show that cues from the social environment may impact the experience of symptoms. Most evidence stems from the induction of contagious itch in experimental settings, for instance, while listening to a lecture or watching videos of people scratching. Research on the extent to which these concepts may translate towards clinical practice, or on how such cues may impact symptom experience in daily life, is lacking. Future research may consider further investigating the influence of social and contextual cues on treatment efficacy in clinical populations. In addition, future research may further investigate which (combination of) mechanisms would be most effective in inducing placebo and nocebo effects for a variety of symptoms across dermatological conditions. Clinical relevance and applicability may be considered here, and the mechanisms that are most promising to establish longer-term effects should have precedence over those that appear to elicit short-term changes. Conditioned dose reduction may be a promising approach, as this method is based on conditioning principles [100], could be considered most directly applicable in clinical practice [101], and has been found to be as effective as full medication doses – not just in psoriasis, but also in other conditions such as attention-deficit hyperactivity disorder [79,102]. Likewise, open-label placebo effect induction may be investigated further in the future. Even though this has been investigated only infrequently in relation to dermatological symptoms or conditions [59,75,76,103,104], research from various other fields further supports the notion that placebo effects can be elicited even when it is known that an inert substance is given [9-13]. Information derived from these studies may pave the way for new therapeutic possibilities, for example the development of psychoeducation regarding the role of expectations and learning in health and disease, or the development of a training specifically targeting the patients' expectations of treatment, and in turn treatment effects. Open-label placebo effects may be a way to ethically apply placebo and nocebo effects in clinical practice [105]. The available body of evidence for open-label placebo effects within dermatology is currently

limited, however, and more research is necessary as a consequence, especially in patient populations.

In addition to utilizing placebo effects in clinical practice, attention should be given to the occurrence of nocebo effects as well. The current review demonstrates that these can be evoked by a variety of methods, and attention should be given to ways to reduce their impact in clinical practice. Some work already shows that previously learned nocebo effects for itch can be reduced by a combination of suggestions and counterconditioning [61]. Studies in other research areas (e.g., in the field of pain) also show promising results for such methods [106]. Suggestions and counterconditioning may, for example, be used to reduce the occurrence of unwanted side effects, or to counter diminished treatment efficacy due to previously learned negative associations [106]. The efficacy of these methods in reducing nocebo effects for itch-related symptoms of the skin and mucous membranes should be researched more extensively in the future.

Placebo and nocebo effects in symptoms and medical conditions are known to vary between individuals. For example, a study investigating pharmacological conditioning of anti-allergic effects demonstrated that symptoms in both conditioned and sham-conditioned groups were likely influenced by the participants' own expectations and cognitions, as these differed from a natural history group [78]. Likewise, there is evidence that individual characteristics, such as personality characteristics and polymorphisms in genetic markers, may impact placebo and nocebo effects [7,107-110], although evidence for these specific predictors of placebo and nocebo effects within the field of dermatology is limited and mixed [8]. Of the studies included in the current review, few investigated predictive factors for placebo or nocebo responding. Some work illustrated that placebo and nocebo responses may have occurred in subgroups only, such as highly hypnotizable or suggestible individuals [73,74]. Likewise, the individual characteristics of the person who is providing information about a treatment (e.g., warmth and competence of a health care provider) may impact the size of effects [24]. Future research could aim to further investigate what factors may impact placebo and nocebo effects in order to provide a more complete and structured picture of under which circumstances these effects are likely to be most strong.

Limitations of the current review were the heterogeneity of the included studies, which prevented a meta-analysis of study results. In addition, some studies have demonstrated high risk of bias, most notably in inclusion of participants (studies on hypnosis selected on high hypnotizability), or in blinding (experimenters providing verbal suggestions were not

blinded and often examined outcomes as well). Moreover, in most articles that described animal research, information needed to rate bias was lacking. As a result, most studies were rated as being unclear on bias. In addition, sample sizes reported in most studies included in this review are small. As such, effects that are small may not have been detected in these studies. Finally, some of the included studies describe experimentally elicited pain. These tests were incidentally included as they occurred alongside an itch induction test or in a relevant patient sample. However, the review did not systematically include pain-induction tests, so the number of studies finding placebo and nocebo effects for pain, as described here, might not reflect the actual incidence of placebo and nocebo effects studied within the field of pain. For a review on those studies see, for example, Peerdeman and colleagues [7].

Overall, this review provides considerable evidence for placebo and nocebo effects within dermatological conditions, specifically for itch and other symptoms of the skin and mucous membranes associated with itch. Such effects can be elicited using various methods, most importantly, by using verbal suggestions, conditioning, or social induction. Some caution is needed in translating this work to clinical practice and more research is needed for a more robust foundation upon which clinical applications may be built. First and foremost, it is important to structurally investigate how variations in induction methods may impact placebo and nocebo effects, and whether all symptoms and medical conditions may be influenced similarly by placebo and nocebo effects elicited through these induction methods. Second, the impact of external factors (e.g., predictors such as suggestibility) on placebo and nocebo effects should be investigated more extensively. Finally, more research is needed to implement this knowledge about placebo and nocebo effects in clinical practice: clinical trials may further explore whether conditioning may be used to maximize placebo effects and minimize nocebo effects in clinical practice, to enhance treatment efficacy, reduce medication intake, and enhance patients' quality of life.

MATERIALS AND METHODS

A complete overview of the methods for the systematic review is provided in the **Supplementary Material**. In short, this review was conducted in accordance with the PRISMA statement on systematic reviews [111] and pre-registered in Prospero (PROSPERO 2018: CRD42018096636). Articles were included in the review if they (1) were conducted in healthy volunteers, animals, or patients with chronic or acute itch associated with a dermatological condition, or associated with (atopic) symptoms of the

skin or the mucous membranes related to itch; (2) investigated experimentally-induced placebo or nocebo effects (e.g., elicitation of effects through conditioning, or social or verbal expectation induction methods such as suggestions); (3) were written in English, Dutch or German; (4) presented new data; and (5) assessed outcomes including – but not limited to – perceived itch, behavioral measures related to itch (e.g., scratching behavior), self-reported symptoms (e.g., allergic or atopic symptoms), extent of neurogenic inflammation, or itch-related inflammatory markers (e.g., histamine, substance P). Articles were excluded when data was presented on a case-by-case descriptive level or when total sample size was $n<5$.

PubMed, PsycInfo, and Embase databases were searched for relevant articles on May 8, 2018. Two independent raters (SM, CvL) screened titles for the inclusion criteria. Next, the two raters assessed abstracts and full-texts for eligibility, using a hierarchical approach. Discrepancies between the two raters were resolved by discussion with a third independent rater (HvM). The reference lists from the included articles were checked for additional relevant articles by both independent raters. Data from the included articles were extracted by one rater (SM) using a piloted form. Two independent raters (SM, KB) assessed risk of bias of each study using the Cochrane risk of bias tool [112]. The SYRCLE risk of bias tool was used for articles describing animal research [113], as were the guidelines described by O'Connor and Sargeant [114].

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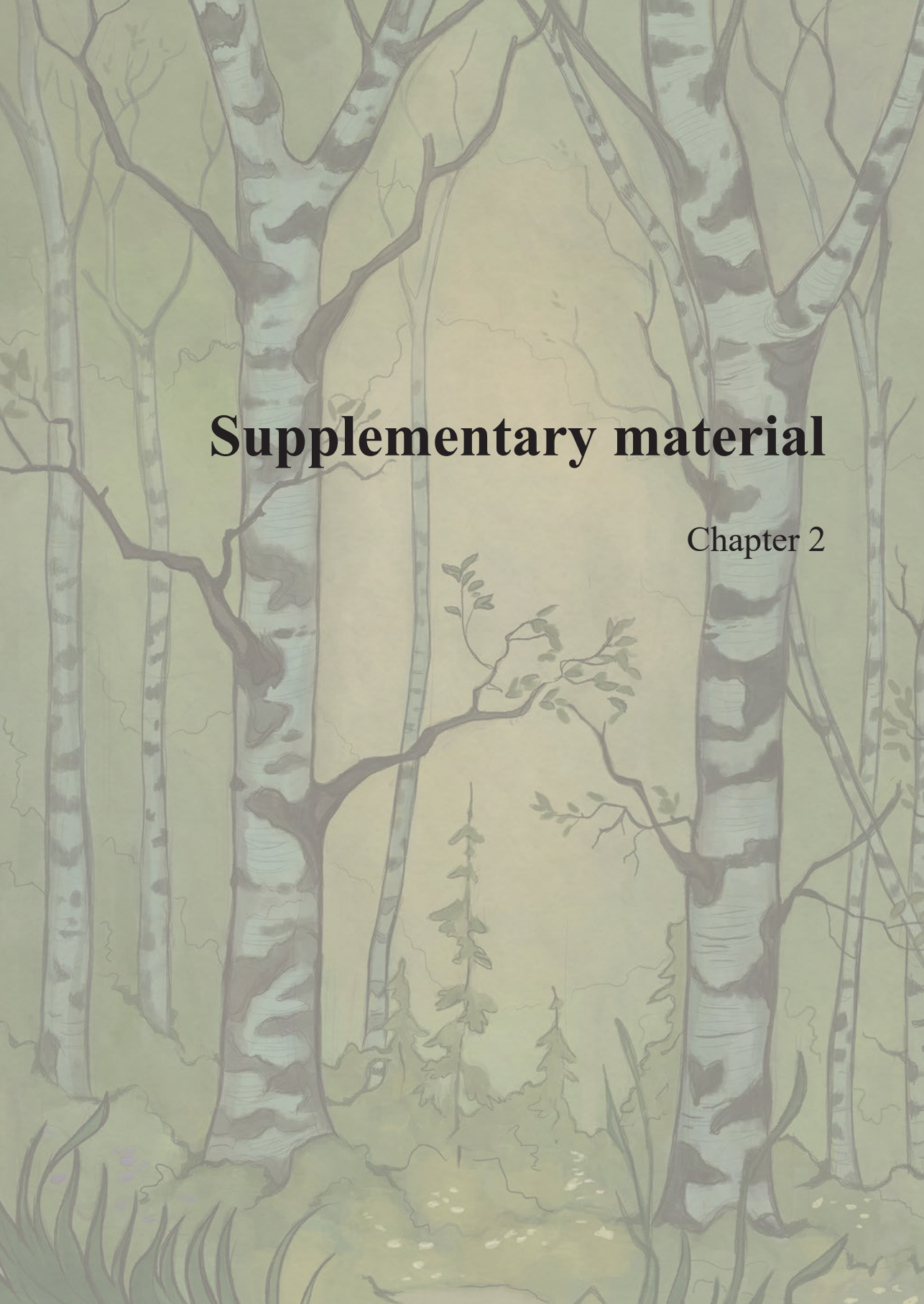


Supplementary material

Chapter 2

SUPPLEMENTARY METHODS

Elaboration on the search strategy

The inclusion criteria were transformed into a systematic search strategy consisting of Medical Subject Headings (MeSH) and title or abstract text words (tiab), that combined placebo or nocebo induction-related terms with (1) methods of experimental itch elicitation, (2) dermatological conditions associated with itch, or (3) eligible types of outcome parameters. The search was conducted in the PubMed, PsycInfo, and Embase databases on May 8th 2018, with search strategies for PsycInfo and Embase being derived from the PubMed strategy (see **Supplementary Figure S6** for the search strategy).

Parameters extracted from the articles

The following categories of parameters were extracted from the articles: 1) self-reported parameters (when self-report measures were not directly related to the intended placebo or nocebo induction, the experimental model used or the medical condition assessed, they were not included); 2) behavioral parameters; and 3) physiological parameters. In addition, descriptives of the included articles were extracted by piloted forms.

Risk of Bias assessment

The SYRCLE risk of bias tool was used by two independent raters (SM, KB) for articles describing animal research [1] together with the guidelines provided by O'Connor and Sargeant [2]. Assessed criteria were: selection bias (clarity of the description in regard to a. random sequence generation, b., baseline characteristics of animals, and c. concealment of group allocation), performance bias (clarity of description for a. random housing of animals, and b. the blinding of personnel and participants), detection bias (clarity of the description of the blinding of outcome assessments), attrition bias (description of incomplete outcome data), reporting bias (whether selective reporting occurred), and other bias (not specified before). Risk of bias of each human study was assessed using the Cochrane risk of bias tool [3]. Ratings of both independent raters were compared, and discrepancies between ratings were resolved by discussion. The following criteria were assessed: selection bias (clarity of the description in regard to a. random sequence generation, and b. concealment of group allocation), performance bias (clarity of description for the blinding of personnel and participants), detection bias (clarity of the description of the blinding of outcome assessments), attrition bias (description of

incomplete outcome data), reporting bias (whether selective reporting occurred), and other bias (not specified before). For both human and animal studies, each category was scored as ‘low RoB’ when the provided information was enough to suspect low bias, ‘high RoB’ when information was mentioned that would incur bias (e.g., insufficient blinding), or ‘unclear RoB’ when information was not clearly provided. Risk of bias analyses were descriptive: no further steps were undertaken to conduct sensitivity analyses or to exclude studies based on risk of bias ratings.

Supplementary Table S1. Brief summary of the methods and results of the included studies.

Population	Total no. of studies	Type of induction	Learning mechanism(s)	Outcome measure(s) category	Proportion of hypo-theses confirmed/k studies per outcome	% confirmed
Animals	8	Placebo	Conditioning	Behavioral	6 / 6	100
				Physiological	8 / 8	100
	17	Nocebo	Conditioning	Behavioral	5 / 7	71
				Physiological	10 / 11	91
	2	Nocebo	Operant conditioning	Behavioral	1 / 2	50
	4	Nocebo	Social induction	Behavioral	2 / 4	50
Healthy participants	7	Placebo	Verbal suggestions + hypnosis	Self-reported	1 / 1	100
				Physiological	4 / 7	57
	6	Placebo	Verbal suggestions	Self-reported	2 / 5	40
				Physiological	1 / 6	17
	1	OL placebo	Verbal suggestions	Self-reported	0 / 1	0
				Physiological	0 / 1	0
	2	Placebo	Conditioning (+ verbal suggestions)	Self-reported	2 / 2	100
	1	Nocebo	Verbal suggestions	Self-reported	1 / 1	100
				Physiological	1 / 1	100
	1	Nocebo	Conditioning (+ verbal suggestions)	Self-reported	3 / 3	100
				Physiological	1 / 1	100
	3	Nocebo	Social induction (e.g., contagious itch by video of people scratching)	Self-reported	3 / 3	100
				Behavioral	3 / 3	100
Patients	12	Placebo	Verbal suggestions + hypnosis	Self-reported	3 / 4	75
				Physiological	3 / 10	30
	2	OL placebo	Verbal suggestions (+ inert pill)	Self-reported	2 / 2	100
	3	Placebo	Pharmacological conditioning / conditioned dose reduction	Self-reported	1 / 3	33
				Physiological	2 / 3	67
	1	Placebo	Conditioning (+ verbal suggestions)	Self-reported	1 / 1	100
	1	Placebo	Social induction (advertising)	Physiological	1 / 1	100
	1	Nocebo	Verbal suggestions + hypnosis	Physiological	1 / 1	100
	4	Nocebo	Verbal suggestions	Self-reported	1 / 1	100
				Physiological	3 / 4	75
	5	Nocebo	Conditioning [a]	Self-reported	0 / 2	0
				Physiological	2 / 3	67
	5	Nocebo	Social induction (e.g., contagious itch by video of people scratching)	Self-reported	5 / 5	100
				Behavioral	4 / 4	100
				Physiological	0 / 1	0

General summary of the proportion of positive results for the studies above (summarized across type of induction and learning mechanisms involved)

Population	Total no. of studies	Type of induction	Learning mechanism(s)	Outcome measure(s) category	Proportion of hypo-theses confirmed/k studies per outcome	% con-firmed
Animals	31	All types	All mechanisms	Behavioral	14 / 19	74
				Physiological	18 / 19	95
Healthy participants	21	All types	All mechanisms	Self-reported	10 / 14	71
				Behavioral	3 / 3	100
				Physiological	7 / 16	44
Patients	34	All types	All mechanisms	Self-reported	13 / 18	72
				Behavioral	4 / 4	100
				Physiological	12 / 23	52

Note. Total no. of studies is the number of studies on the same type of induction (e.g., placebo). The 'k studies per outcome' in the column of proportion of hypotheses confirmed refers to the number of studies measuring that specific category of outcomes. Some studies report multiple experiments (e.g., follow-up experiments) or multiple outcomes of the same type (e.g., more than 1 self-report measure). For these studies, a hypothesis was considered confirmed when the average across experiments or outcomes indicated effective placebo or nocebo induction.

OL = open-label (non-concealed placebo effect induction). [a] Two out of five studies (Jordan, 1972, and Robertson, 1975) compared the efficacy of conditioning scratch responses for patients and healthy controls. While it was concluded that scratch responses were more easily conditioned in patients, no remarks regarding the efficacy of conditioning itself were made (i.e. no comparisons with control groups / a non-conditioned state). As such, these were not counted amongst the proportional positive results (confirmed hypotheses) in the table.

Supplementary Table S2. Overview of animal studies.

Author, year	*Subjects species (n, sex)*	*Study design*	*Category*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
I. Conditioned immunosuppression						
Ader, 1975 [4]	Charles River rats (96, male)	Between-subjects	Conditioned immunosuppression	Conditioning of a saccharin drinking solution (SAC, conditioned stimulus; CS) and a cyclophosphamide injection (CY, unconditioned stimulus; UCS), as tested by a delayed-type hypersensitivity response (DTH) sensitization to sheep red blood cells (SRBC)	1) Conditioned groups: a) CS_0 (not re-exposed to CS) b) CS_1 (conditioned, re-exposed once) c) CS_2 (conditioned, re-exposed twice) d) UCS (re-exposed once to UCS) 2) Non-conditioned control 3) Placebo group	▪ SAC preference in CS_1 and CS_2 groups: ↓ ▪ DTH response to SRBC: hemagglutination (antibody) titers in CS_1 and CS_2 groups: ↓
Bovbjerg, 1987 [5]	Mice (61, male)	Randomized controlled trial, between-subjects	Conditioned immunosuppression	Conditioning of SAC (CS) and CY (UCS), as tested by a DTH sensitization to SRBC	1) Conditioned groups: a) CS_r (experimental) b) CS_{0r} (not re-exposed) c) UCS (re-exposed to UCS) 2) Non-conditioned control 3) Placebo group	DTH response to SRBC: paw swelling in CS_r groups vs. controls: ▪ 1st exposure ↓, ▪ 2nd + 3rd exposures ↑
Exton, 2000 [6] *Experiment 1*	Dark agouti rats (30, male)	Randomized controlled trial, between-subjects	Conditioned immunosuppression	Conditioning of SAC (CS) and cyclosporine-A (CSA; UCS), as tested by a DTH sensitization to 2,4-dinitrochlorobenzene (DNCB)	1) conditioning 2) sham-conditioned 3) CSA exposed	▪ SAC preference after conditioning: ↓ ▪ DNCB-induced ear swelling after conditioning: ↓
Exton, 2000 [6] *Experiment 2*	Dark agouti rats (30, male)	Randomized controlled trial, between-subjects	Conditioned immunosuppression *following splenic denervation*	Conditioning of SAC (CS) and CSA (UCS), as tested by a DTH sensitization to DNCB	1) Sham conditioned, sham denervated 2) Sham conditioned, denervated 3) Conditioned, not denervated 4) Conditioned, denervated 5) CSA treated, denervated	▪ SAC preference after conditioning: ↓ ▪ DNCB-induced ear swelling after conditioning: ↓ ▪ Effects of splenic denervation on conditioning: n.s.
Kelley, 1985 [7] *Experiment 1*	Balb/c mice (60, female)	Between-subjects	*n/a*	Testing of the effects of lithium (LiCl) on DTH response, as tested by a DTH sensitization to SRBC	1) Immunized animals 2) Non-immunized animals	▪ No effects of LiCl on DTH-induced footpad swelling (as assessed by footpad thickness)

Supplementary Table S2 *(continued 2/11)*

Author, year	*Subjects species (n, sex)*	*Study design*	*Category*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Kelley, 1985 [7] *Experiment 2*	Balb/c mice (33, female)	Between-subjects	Conditioned immunosuppression	Conditioning of SAC (CS) and an injection of LiCl (UCS), as tested by a DTH sensitization to SRBC	1) Placebo: SAC + saline, immunized 2) Non-conditioned: water + LiCl, immunized 3) Conditioned: SAC + LiCl, immunized 4) Placebo: SAC + saline, non-immunized 5) Non-conditioned: water + LiCl, non-immunized 6) Conditioned: SAC + LiCl, non-immunized	▪ SAC preference (measured by SAC intake) in immunized conditioned animals: ↓ ▪ DTH-induced footpad swelling (as assessed by footpad thickness) in immunized conditioned animals: ↓
Kelley, 1985 [7] *Experiment 3*	Balb/c mice (30, female)	Between-subjects	*n/a*	Testing whether conditioned effects on DTH in experiment 3 could have been caused by water deprivation, as tested by a DTH sensitization to SRBC	1) Water-deprived, DTH tested, immunized 2) Non-water-deprived, DTH tested, immunized 3) Water-deprived, DTH tested, non-immunized 4) Non-water-deprived, DTH tested, non-immunized	▪ Differences in DTH-induced footpad swelling (as assessed by footpad thickness) between groups: n.s.
Kelley, 1985 [7] *Experiment 4*	Balb/c mice (24, female)	Between-subjects	Conditioned immunosuppression	Conditioning of SAC (CS) and an injection of LiCl (UCS), as tested by a DTH sensitization to SRBC	1) Placebo: SAC + saline, immunized 2) Non-conditioned: water + LiCl, immunized 3) Conditioned: SAC + LiCl, immunized 4) Placebo: SAC + saline, non-immunized 5) Non-conditioned: water + LiCl, non-immunized 6) Conditioned: SAC + LiCl, non-immunized	▪ SAC preference (measured by SAC intake) in immunized conditioned animals: ↓ Plasma glucocorticoids in immunized conditioned animals: ↑
Mei, 2000 [8]	LACA mice & Wistar rats (36, male mice & female rats)	Randomized controlled trial, between-subjects	Conditioned immunosuppression	Conditioning of camphor odor (CAM, CS) and an intraperitoneal injection of CY (UCS), as tested by a DTH sensitization to DNCB	1) CR (conditioned) 2) UCR control 3) DTH control 4) DTH- control 5) CY control 6) CAM control	▪ Left/right ear weight ratio (as index of DTH response) after conditioning: ↓ Leukocyte migration inhibition (assessed by leukocyte migration inhibitory factor/LMIF) after conditioning: ↑

Supplementary Table S2 *(continued 3/11)*

Author, year	*Subjects species (n, sex)*	*Study design*	*Category*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Rogers, 1976 [9]	Sprague-Dowley rats (80, male)	Between-subjects	Conditioned immunosuppression	Conditioning of SAC (CS) and an intraperitoneal injection of CY (UCS), as tested by a DTH sensitization to SRBC	1) conditioned (n=50): a) CS_0: no re-exposure b) CS_1: re-exposure once c) CS_2: re-exposed twice d) UCS: re-exposed to UCS only 2) non-conditioned (n=10) 3) placebo (PLA; n=10)	SAC preference in conditioned (CS_i) groups: ↓ ▪ DTH (assessed by hemagglutination/antibody titers) ↓ in CS_2 and UCS, compared to CS_1, CS_0 an control groups
Roudebush, 1991 [10]	Balb/c mice (*n* unknown, male)	Randomized controlled trial, within-between-subjects	Conditioned immunosuppression	Conditioning of SAC (CS) and CY or dexamethasone (DEX; UCS), as tested by a DTH sensitization to corticosterone	1) DTH negative 2) DTH positive 3) Conditioned 4) Non-conditioned 4) Other controls	Saccharin preference after conditioning with CY and DEX ↓ DTH-induced paw swelling after conditioning when CY=UCS ↓; when DEX=UCS n.s.
Wayner, 1978 [11] *Experiment 1*	Wistar derived albino rats (84, male)	Between-subjects	Conditioned immunosuppression	Conditioning of SAC (CS) and CY (UCS), as tested by a DTH sensitization to SRBC *In experiment 1, animals were sensitized to a T-cell **dependent** antigen: sheep red blood cells (SRBC)*	1) Conditioned: a. UCS: re-exposed to UCS once b. CS_0: not re-exposed to CS or UCS c. CS_1: CS re-exposed once d. CS_2: CS re-exposed twice e. CS_3: CS re-exposed thrice 2) Non-conditioned 3) PLA	▪ SAC preference ↓ in conditioned groups compared to baseline DTH response to SRBC – hemagglutination (antibody) titers: ▪ CS_1 & CS_2 ↓ than NC & CS_0; ▪ CS_1 & CS_2 compared to UCS: n.s.; CS_3 compared to all: n.s.
Wayner, 1978 [11] *Experiment 2*	Wistar derived albino rats (84, male)	Between-subjects	Conditioned immunosuppression	Conditioning of SAC (CS) and CY (UCS), as tested by a DTH sensitization to Bruscella (B.) Abortus *In experiment 2, animals were sensitized to a T-cell **independent** antigen: B. Abortus*	1) Conditioned: a. UCS: re-exposed to UCS once b. CS_0: not re-exposed to CS or UCS c. CS_1: CS re-exposed once d. CS_2: CS re-exposed twice e. CS_3: CS re-exposed thrice 2) Non-conditioned control 3) PLA	▪ SAC preference ↓ in conditioned groups compared to baseline DTH response to B. Abortus – hemagglutination (antibody) titers: ▪ *UCS excluded from analysis.* ▪ PLA + CS_3 ↑ than other groups ▪ NC, CS_0, CS_1, CS_2: n.s.

Supplementary Table S2 *(continued 4/11)*

Author, year	*Subjects species (n, sex)*	*Study design*	*Category*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
II. Conditioned allergic response						
Dark, 1987 [12] *Experiment 1*	Guinea pigs (24, male)	Randomized controlled trial, between-subjects	Conditioned allergic response	Conditioning of bovine serum albumin (BSA; UCS) to odor of dimethylsulfide or triethylamine (CS+/CS-)	1) stressed conditioned 2) non-stressed conditioned	Histamine release (assessed by blood serum level): ▪ stressed: post-conditioning ↑ ▪ non-stressed: n.s.
Dark, 1987 [12] *Experiment 2*	Guinea pigs (15, male)	Randomized controlled trial, between-subjects	Conditioned allergic response	Conditioning of BSA (UCS) to odor dimethylsulfide (CS)	1) conditioned 2) unpaired	Histamine release (assessed by blood serum level): ▪ post-conditioning: ↑
Djuric, 1987 [13] *Experiment 1*	Wistar rats (66, female)	Randomized controlled trial, between-subjects	Conditioned allergic response	Conditioning of ovalbumin (OA; UCS) to saccharin (CS)	Control groups 1) non-immunized SAC-OA 2) non-immunized SAC-OA with pre-exposure 3) immunized SAC-OA with pre-exposure 4) immunized, OA, no CS 5) immunized, SAC, no UCS Conditioned groups 6) immunized, SAC-OA (2mg) 7) immunized, SAC-OA (1mg, late evocation) 8) immunized, SAC-OA (1mg)	▪ Anaphylactic shock behavior post-conditioning: ↑ ▪ SAC preference post-conditioning: ↓
Djuric, 1987 [13] *Experiment 2*	Wistar rats (36, female)	Randomized controlled trial, between-subjects	Conditioned allergic response	Conditioning of OA (UCS) to saccharin (CS) for different retention periods	1) water-OA, no CS, 4 weeks rentention 2) water-OA, no CS, 8 weeks rentention 3) SAC + OA (2mg), 4 weeks rentention 4) SAC + OA (2mg), 8 weeks rentention	▪ Anaphylactic shock behavior after conditioning: ↑ ▪ SAC preference after conditioning: ↓ ▪ Effects of rentention period: n.s.
Djuric, 1988 [14]	Wistar rats (73, 53% male)	Between-subjects	Conditioned allergic response	Conditioning of OA (UCS) to saccharin (CS) with different dosages of OA	1) 0.0 mg OA (control) 2) 0.5 mg OA ($CS_{0.5}$) 3) 1.0 mg OA ($CS_{1.0}$) 4) 2.0 mg OA ($CS_{2.0}$) 5) 3.0 mg OA ($CS_{3.0}$)	▪ Anaphylactic shock behavior after conditioning: ↑ in parallel with the increase in OA dosage ▪ SAC preference following conditioning: ↓ as function of OA dosage

Supplementary Table S2 *(continued 5/11)*

Author, year	*Subjects species (n, sex)*	*Study design*	*Category*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Irie, 2001 [15] *Experiment 1*	Guinea pigs (20, male)	Randomized controlled trial, between-subjects	Conditioned allergic response	Conditioning of OA (UCS) to an odor of dimethylsulfide (CS)	1) conditioned group: CS-UCS paired presentation 2) unconditioned group: unpaired presentation of CS or UCS	▪ Plasma histamine levels following conditioning: ↑
Irie, 2001 [15] *Experiment 2*	Guinea pigs (37, male)	Randomized controlled trial, between-subjects	Conditioned allergic response *(with and without anesthesia)*	Conditioning of OA (UCS) to an odor of dimethylsulfide (DMS; CS) or triethylamine (TEA, CS)	1) Conditioned, CS exposed (DMS), no UCS (antigen) 2) Conditioned, CS exposed (TEA), no UCS 3) Conditioned, saline exposed, no UCS 4) Unconditioned, CS exposed, no UCS 5) Conditioned, UCS exposed 6) Conditioned, CS+UCS exposed	▪ Plasma histamine levels: n.s. ▪ Bronchoalveolar lavage fluid (BALF) histamine levels: n.s. ▪ Lung tissue histamine levels: ↑ in DMS group compared to TEA group
Irie, 2002a [16] *Part 1*	Guinea pigs (34, male)	Randomized controlled trial, between-subjects	Conditioned allergic response *(with and without fasting stress induction)*	Conditioning of ovalbumin (UCS) to an odor of dimethylsulfide (CS)	1) Conditioned + feeding 2) Conditioned + fasting 3) Control (uncoupled UCS/CS presentation + feeding)	▪ Plasma histamine levels following conditioning: ↑ for fasting groups only
Irie, 2002a [16] *Part 2*	See Irie, 2002a part 1	Controlled trial, between-subjects (repeat of part 1 after 1 month, in which animals were reconditioned)	Conditioned allergic response *(with and without fasting stress induction)*	Conditioning of ovalbumin (UCS) to an odor of dimethylsulfide (CS)	1) Conditioned + fasting 2) Conditioned + feeding 6) Control (uncoupled UCS/CS presentation + feeding) *Feeding and fasting animals were switched compared to part 1*	▪ Plasma histamine levels following conditioning: n.s. ▪ Respiratory resistance: n.s. ▪
Irie, 2002b [17]	Guinea pigs (40, male)	Randomized controlled trial, between-subjects	Conditioned allergic response *(with and without isolation)*	Conditioning of ovalbumin (UCS) to an odor of dimethylsulfide (CS)	1) Conditioned, alone (acq), paired (evoc) 2) Conditioned, alone (acq), alone (evoc) 3) Conditioned, paired (acq), alone (evoc) 4) Conditioned, paired (acq),paired (evoc) 5) Control, paired	▪ Plasma histamine levels following conditioning: ↑ in groups 1, 2, 4 ▪ Plasma histamine levels in group 4 ↑ than in group 1, 3 and control ▪ Main effect of isolation: n.s.
Irie, 2004 [18]	Guinea pigs (24, male)	Randomized controlled trial, between-subjects	Conditioned allergic response *(with and without diazepam administration)*	Conditioning of ovalbumin (UCS) to an odor of dimethylsulfide (CS)	1) Conditioned, diazepam given on evocation day 1+2, saline on 3 2) Conditioned, saline given on evocation day 1, diazepam on 2+3	▪ Plasma histamine levels on day 1 following conditioning: ↑ only after saline, ▪ Group differences on evocation day 2+3: n.s.

Supplementary Table S2 *(continued 6/11)*

Author, year	*Subjects species (n, sex)*	*Study design*	*Category*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
MacQueen, 1989 [19]	Rats (43, sex not described)	Randomized controlled trial, between-subjects	Conditioned allergic response	Conditioning of a subcutaneous injection of egg albumin (EA, UCS) to an audiovisual cue (AV, CS)	1) Paired (conditioned) 2) Unpaired control 3) Negative control (placebo only) 4) Positive control (AV+EA)	▪ Rat Mast Cell Protease II (RMCP II) after conditioning: ↑
Markovic, 1988[20] *Experiment 1*	Wistar rats (24, female)	Randomized controlled trial, between-subjects	Conditioned allergic response	Conditioning of ovalbumin (OA, UCS) given intraperitoneally (ip) to a saccharin solution (SAC, CS)	1) CS-US group (immunized, CS-UCS) 2) Non-immunized rats, presented with a CS-UCS pairing (n.i. control) 3) US-only control (immunized , no CS) 4) CS-only control (immunized , no UCS)	▪ SAC preference after conditioning: ↓
Markovic, 1988[20] *Experiment 2*	Wistar rats (46, female)	Randomized controlled trial, between-subjects	Conditioned allergic response	Conditioning of OA (UCS) given intraveneously (iv) to a saccharin solution (SAC, CS)	1) CS-US group (immunized, CS-UCS) 2) Non-immunized rats, presented with a CS-UCS pairing (n.i. control) 3) US-only control (immunized , no CS) 4) CS-only control (immunized , no UCS)	▪ SAC preference after conditioning: ↓
Markovic, 1988[20] *Experiment 3*	Wistar rats (49, female)	Randomized controlled trial, between-subjects	Conditioned allergic response	Conditioning of OA (UCS) to an isotonic 3.16% sodium saccharin solution (CS) that was injected iv together with UCS	1) CS-US group (immunized, CS-UCS) 2) Non-immunized rats, presented with a CS-UCS pairing (n.i. control) 3) US-only control (immunized , no CS) 4) CS-only control (immunized , no UCS)	▪ SAC preference after conditioning: ↓
Peeke, 1987a [21]	Guinea pigs (24, male)	Randomized controlled trial, within-between-subjects	Conditioned allergic response *(with and without stress induction)*	Conditioning of bovine serum albumin (BSA; UCS) to an odor (triethylamine or dimethylsuldife; 50/50 rate for being CS+ or CS-)	1) Handled (stressed) conditioned 2) Non-handled conditioned	▪ Difference between CS+ and CS- presentation: ▪ plasma histamine level ↑ for CS+ in handled group; in non-handled group n.s. ▪ plasma cortisol levels ↑ for CS+ in handled group on 1 out of 3 extinction trials. For non-handled group, n.s.

Supplementary Table S2 *(continued 7/11)*

Author, year	*Subjects species (n, sex)*	*Study design*	*Category*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Peeke, 1987b [22]	Guinea pigs (23)	Randomized controlled trial, within-between-subjects	Conditioned allergic response *(with and without pre-treatment with dexamethasone (DEX))*	Conditioning of nebulized bovine serum albumin (BSA; UCS) to an odor (dimethylsulfide, CS)	1) Conditioned with DEX 2) Conditioned w/o DEX 3) Control	▪ plasma histamine level ↑ in conditioned compared to control; with DEX ↑ than w/o. ▪ plasma cortisol levels ↓ in DEX pretreated compared to non-pretreated groups.
Russell, 1984 [23]	Guinea pigs (8, male)	Within-subjects	Conditioned allergic response	Conditioning to an injection of bovine serum albumin (BSA) in the footpad to an odor (triethylamine or dimethylsuldife; 50/50 rate for being CS+ or CS-)	None	Difference between CS+ and CS- presentation: ▪ plasma histamine level ↑
III. Conditioned lung anaphylactic shock						
Justesen, 1970 [24]	Guinea pigs (25, male)	Between-subjects	Conditioned asthmatic response	Conditioning of inhalation of an aerosol (nebulized protein solution, UCS) to aspects of the nebulizer process (i.e., sound, room; CS)	1) Conditioned animals 2) Naïve controls	▪ On 2nd day of conditioning: 3 out of 16 conditioned animals developed a response (asthmatic attack as measured by plethysmographic amplitude). ▪ On 3rd day of conditioning: 10 out of 16 conditioned animals developed response. ▪ On 4th day of conditioning: 16 out of 16 conditioned animals developed response.
Noelpp , 1951a [25]	Guinea pigs (8, sex not described)	Within-subjects	Conditioned lung anaphylactic response	Conditioning of an aerosol (allergen; UCS) to a sound (sound of aerosol nebulizer; CS) in 2 series of 5 acquisitions followed by 1 CS-exposure only (evocation).	None	▪ Asthmatic attack (marked by a change in breathing patterns) after 5 acquisitions: n.s. (1 out of 8 animals responded) ▪ Asthmatic attack after 10 acquisitions: n.s. (3 out of 8 animals responded)

Supplementary Table S2 *(continued 8/11)*

Author, year	*Subjects species (n, sex)*	*Study design*	*Category*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Noelpp, 1951b [26]	Guinea pigs (28, male & female)	Between-subjects	Conditioned lung anaphylactic response	Conditioning of an aerosol (allergen; UCS) to a sound (sound of aerosol nebulizer; CS) in series of 5 acquisitions followed by 1 CS-exposure only (evocation).	1) Light-stressed animals 2) Non light-stressed animals	▪ For asthmatic attack (marked by a change in breathing patterns): Conditioning in stressed group ↑ than non-stressed. ▪ In stressed group 14/14 animals developed asthmatic breathing patterns upon CS-exposure. ▪ Of the non-stressed animals, 2/14 showed a clear response, 3/14 hints of a response (5/14 total).
Ottenberg, 1958 [27]	Guinea pigs (30, male)	Randomized controlled trial, between-subjects	Conditioned lung anaphylactic response	Conditioning of a fine mist of a dilute solution of egg white (UCS) to location (CS).	1) conditioned 2) control	▪ Asthma attacks (marked by use of accessory muscles, gasping, coughing, and pronounced respiratory distress) following egg-white spray: ↑ ▪ *After 3rd time exposure; 20% experienced attacks. During the extinction phase all of this 20 per cent (6 animals) had asthmatic attacks without the presence of egg-white spray. Four animals continued to have attacks through 9 trials. Extinction was apparent in all after 13 trials.*
Palermo-Neto, 2000 [28] *Experiment 1*	Wistar rats (60, male)	Randomized controlled trial, between-subjects	Conditioned lung anaphylactic response	Conditioning of ovalbumin (OA, UCS) as an aerosol to an audiovisual cue (AV, CS)	1) P_1 – paired (conditioned) 2) NC_1 – negative control 3) PC_1 – positive control (exp.1)	▪ Lung anaphylactic response (LAR; as behavior scored by observer on a 0-5 scale) following conditioning in P_1: ↑ ▪ Rearing n.s. ▪ Locomotion frequency: PC_1 ↓ than NC_1; P_1 & NC_1 n.s. ▪ Locomotion, rearing and the plus-maze data following conditioning: n.s. ▪ Corticosterone levels following CS-exposure in PC_1: ↑

Supplementary Table S2 *(continued 9/11)*

Author, year	*Subjects species (n, sex)*	*Study design*	*Category*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Palermo-Neto, 2000 [28] *Experiment 2*	Wistar rats (40, male)	Randomized controlled trial, between-subjects	Conditioned lung anaphylactic response	Conditioning of OA (UCS) as an aerosol to an audiovisual cue (AV, CS)	1) NC_2 – negative control 2) PC_2 – positive control (exp.2) 3) U_2 – unpaired (CS & UCS presented separately) 4) N_2 – naïve control	▪ Rearing: n.s. ▪ Locomotion frequency: PC_2 ↓ than U_2, NC_2 or N_2 ▪ Plus-maze data: % of open arm exploration and time spent in open-arm ↓ in PC_2 compared to U_2, NC_2 or N_2 ▪ Corticosterone levels following CS-exposure in PC_2 ↑ *CS exposure per se induced effects in plus maze data and corticosterone levels; not conditioning*
IV. Operant conditioning of scratching response						
Morgan, 1979 [29] *Experiment 1*	Lister hooded rats (12, female)	Randomized controlled trial, between-subjects	Operant conditioning of scratching behavior	When desirable behavior was presented, a lever with food was presented. A concurrent variable-interval schedule was used.	1) wash-scratch behavior conditioned 2) wash-rear behavior conditioned 3) wash-scratch yoked control 4) wash-rear yoked control	▪ Scratching after operant conditioning: ↑ in wash-scratch than in the wash-rear group. ▪ Comparison with yoked control: n.s.
Morgan, 1979 [29] *Experiment 2*	Lister hooded rats (10, female)	Randomized controlled trial, between-subjects	Operant conditioning of scratching behavior	When desirable behavior was presented, a lever with food was presented. A concurrent variable-interval schedule was used.	1) wash-scratch behavior conditioned 2) wash-rear behavior conditioned 3) wash-scratch yoked control 4) wash-rear yoked control	▪ Scratching after operant conditioning: n.s.
Pearce, 1978 [30] *Experiment 1*	Lister rats (12, male)	Randomized controlled trial, between-subjects	Operant conditioning of scratching behavior	Animals were rewarded with food pellets when showing a bout of scratching behavior. Prior to experiment, animals were food deprived.	1) Scratching conditioned 2) Yoked control (to scratching group) 3) Lever press control	▪ Scratching behavior ↑ in scratching conditioning and lever press groups compared to control.
Pearce, 1978 [30] *Experiment 2*	Lister rats (8, male)	Randomized controlled trial, between-subjects	-	Preparation of experiment 3; testing effects of a collar on scratching. No conditioning took place.	-	-

Supplementary Table S2 *(continued 10/11)*

Author, year	*Subjects species (n, sex)*	*Study design*	*Category*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Pearce, 1978 [30] *Experiment 3*	Lister rats (24, male)	Randomized controlled trial, between-subjects	Operant conditioning of scratching behavior	Animals were rewarded with food pellets when showing a bout of scratching behavior. Prior to experiment, animals were food deprived. *The effects of a collar on operant conditioning were tested.*	1) Scratching conditioned; with collar 2) Yoked control (to scratching group w collar) 3) Scratching conditioned; w/o collar 4) Yoked control (to scratching group w/o collar)	▪ Scratching behavior ↑ in scratching conditioning groups; with collar ↑ compared to w/o collar
Pearce, 1978 [30] *Experiment 4*	Lister rats (12, male)	Randomized controlled trial, between-subjects	Operant conditioning of scratching behavior	The extinction of previously learned scratching bouts was tested. *Conditioned animals of experiment 3 were used.*	1) Scratching conditioned; *collar removed* 2) Scratching conditioned; w/o collar	▪ Difference in scratching behavior between extinction with and w/o collar: n.s.
V. Social induction (contagious scratching)						
Feneran, 2013 [31] *Experiment 1*	Rhesus macaques (16, male)	Within-subjects observational	Social induction (contagious scratching)	Monkeys were paired with another and each pair was observed during 2x20min. All occurrences of scratching were recorded	None	Scratching after cagemate scratched (time elapsed between scratching bout of cagemate and target monkey): ↑
Feneran, 2013 [31] *Experiment 2*	Rhesus macaques (10, male)	Within-subjects, counterbalanced	Social induction (contagious scratching)	Videotapes of monkeys scratching in experiment 1 were presented (also neutral, and passive controls). Scratching in response was measured	None	Scratching episodes when presented with 'scratch video': ↑
Nakayama, 2004 [32]	Japanese monkeys (5, 40% male)	Within-subjects	Social induction (contagious scratching)	The transferability of scratching from a stranger to a target was tested in a time-series experiment. Three test conditions were used that varied as a function of the placement of the stranger and the visibility of the target by conspecific observers: the stranger, no stranger, and obstructed view conditions. Each monkey served as target for 10 trials.	None	▪ Main effect of target behavior (stranger's scratching): n.s. (marginal ↑ scratching). ▪ Scratching by conspecific observers ↑ in the stranger condition than in the no stranger and obstructed view conditions. Target's behavior: effects on scratching by conspecific observers ↑ only in the stranger condition

Supplementary Table S2 *(continued 11/11)*

Author, year	*Subjects species (n, sex)*	*Study design*	*Category*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
						▪
Whitehouse, 2016 [33]	Barbary macaques (6, 33.3% male)	Within-subjects	Social induction (contagious scratching)	10 scratching videos and 10 neutral videos were displayed, with half featured a familiar individual and half featured an unfamiliar individual. Each video was composed of five unique occurrences of scratching (or other neutral behavior) from a single individual.	None	▪ Influence of videos on scratching rate n.s. ▪ Attention to video ↑ for scratching video compared to neutral. ▪ Attention to video ↑ for familiar compared to unfamiliar individual.
Yu, 2017 [34] *Experiment 1*	Mice (14-16)	Randomized controlled trial, between-subjects	Social induction (contagious scratching)	Mice with excessive spontaneous scratching due to chronic itch were used as demonstrators; naïve mice were observers. Mice that did not scratch excessively were used as control demonstrators	1) Scratching group (demonstrators) 2) Control demonstrators 3) Scratching observers 4) Control observers	▪ Scratching behavior ↑ in scratching observers, in control observers n.s. ▪ Looking behavior n.s.
Yu, 2017 [34] *Experiment 2*	Mice (*n* unknown, sex unknown)	Randomized controlled trial, between-subjects	Social induction (contagious scratching)	The dispensability of auditory and olfactory cues for contagious scratching was tested by placing mice in front of a screen displaying a conspecific with scratching behavior. As a control, a video of a mouse that ambulated without scratching was displayed.	1) Scratching observers 2) Control observers	▪ Scratching behavior ↑ in scratching observers, in control observers n.s. ▪ Looking behavior n.s.

Note. acq = acquisition (of conditioned response); AV = audiovisual cue; BALF = bronchoalveolar lavage fluid; B. Abortus = Bruscella Abortus; BSA = bovine serum albumin; CAM = camphor odor; CS = conditioned stimulus; CSA = cyclosporine-A; CY = cyclophosphamide; DEX = dexamethasone; DMS = dimethylsulfide; DNCB = 2,4-dinitrochlorobenzene; DTH = delayed-type hypersensitivity response; EA = egg albumin; evoc = evocation (of conditioned response); ip = intraperitoneally; iv = intravenously; LAR = lung anaphylactic response; LiCl = lithium; LMIF = leukocyte migration inhibitory factor; NC = negative control; n.i. = non-immunized; n.s. = non-significant; OA = ovalbumin; P = paired; PC = positive control; PLA = placebo; SAC = saccharin drinking solution; SRBC = sheep red blood cells; TEA = triethylamine; CS = unconditioned stimulus

Supplementary Table S3. Overview of studies with healthy participants.

Author, year	*Subjects N (sex, age)*	*Study design*	*Category / type of comparison*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
I. Placebo induction (regular)						
a. By verbal suggestions and hypnosis						
Black, 1963b [35]	14	Within-subjects	Placebo	Verbal suggestions (VS) about decrease in response to allergen (horse serum), and hypnosis	None	Wheal area (Prausnitz-Küstner reaction to horse serum): ▪ ↓ following VS (as a function of depth of trance after hypnosis)
Laidlaw, 1996 [36]	38 (34.2% male, M_{age}= 39.2)	Within-subjects	Placebo	Participants were asked to use their imagination to become nonreactive to skin tests. Various possibilities were given under hypnosis for calming skin reactions to histamine (e.g., imagining a protective layer on or changes in the skin). In addition, direct VS of nonreactivity, coolness and dissociation were given.	None	Within-group pretest, control & intervention comparisons: ▪ Wheal areas following intervention compared to control: ↓ ▪ Titration gradients following intervention compared to control: ↓ ▪ Titration endpoint data: n.s.
Locke, 1987 [37]	12 *+ 30 non-hospitalized controls*	Within-subjects	Nocebo vs. placebo	Participants received one of the following verbal suggestions: 1) that the right arm (RA) would show an enhanced response to one of seven antigens (tetanus toxoid, diptheria toxoid, Streptococcus, tuberculin, Candida. Trichophyton, and Proteus), and the left arm (LA) was control; 2) that RA would show a suppressed response, LA control; 3) that RA was control, LA enhanced; or 4) RA control, LA suppressed. Suggestions were given under hypnosis. Audiotape reinforcement was practiced prior to testing.	1) RA enhanced 2) RA suppressed 3) LA enhanced 4) LA suppressed 5) 30 control subjects	▪ Skin test responses (measured as wheal/erythema (flare) ratio) after hypnosis and VS between groups differences: n.s.

Supplementary Table S3 *(continued 2/8)*

Author, year	*Subjects N (sex, age)*	*Study design*	*Category / type of comparison*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Locke, 1994 [38]	24 (45.8% male, M_{age}= 22.0) *Participants were pre-selected on the basis of being able to influence skin temperature under hypnosis*	Within-subjects	Nocebo vs. placebo	Participants were told that highly hypnotizable persons are usually able to increase and decrease their peripheral skin temperature during hypnosis using images associated with cold or warmth. The images of immersing the hand in hot water and ice water were used unless the subjects offered particularly vivid images of their own. Participants were then given suggestions to influence their skin response to varicella-zoster (VZ) antigen. Suggestions were given under hypnosis.	1) No hypnosis 2) Hypnosis, no suggestions 3) Hypnosis, suggestions to suppress 4) Hypnosis, suggestions to enhance	▪ Skin response to VZ antigen (swelling/induration) after hypnosis and VS between groups differences: n.s.
Zachariae, 1989 [39]	18 (72.2% male) *Experimental group was preselected for being highly susceptible for hypnosis*	Between-subjects	Placebo vs. nocebo	Suggestions (VS) were given that the reaction to histamine / Mantoux test would be less than before for the right arm, and that the reaction for the left arm would increase. VS were given under hypnosis. Participants were given an audio tape containing hypnotic induction and guided imagery instructions repeating the VS. They were instructed to use the tape twice daily during 72h.	1) highly hypnotizable 2) controls	▪ Histamine flare ↓ following positive VS, and ↑ for negative VS. ▪ Histamine wheal n.s. (for pos. vs. neg.) <u>Mantoux skin responses:</u> ▪ Difference between positive VS and negative VS areas ↑ for both erythema size and induration ▪ Differences between positive VS and negative VS in the control group: n.s.
Zachariae, 1990 [40]	10 (50.0% male) *Preselected for being highly susceptible for hypnosis*	Within-subjects	Placebo	VS of analgesia in the right hand and arm were given.	None	▪ After hypnosis/suggestions: mean reduction in pain (from laser stimulation & from histamine skin prick) was 71.7% ▪ Laser-induced pain related brain potentials ↓during hypnosis/suggestions ▪ Flare response to histamine ↓ during hypnosis/suggestions compared to pre- and post-measurements

Supplementary Table S3 *(continued 3/8)*

Author, year	*Subjects N (sex, age)*	*Study design*	*Category / type of comparison*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Zachariae, 1993 [41]	20 (60.0% male, M_{age}= 29.5)	Within-subjects	Placebo vs. nocebo	In a 2x2 design, participants had dinitrochlorobenzene (DNCB) and diphenylcyclopropenone (DCP) placed on either the left or right arm for a delayed-type hypersensitivity response (DTH). Participants had their arms marked with red (indicating the reaction should be increased) and blue (indicating the reaction should be decreased) (balanced).	None	▪ Effect of suggestions on DTH skin responses (erythema, skin thickness): n.s.
b. By verbal suggestions only						
Darragh, 2013 [42]	58 (27.6% male, M_{age}= 20.3)	Randomized-controlled between-subjects	Placebo	VS about to-be-expected skin response to histamine after application of a (sham) antihistamine cream	1) Placebo VS 2) Control	▪ Expected wheal area: ↓ ▪ Wheal area following VS: n.s. ▪ Heart rate (HR) following VS: ↓ ▪ Heart rate variability (HRV) following VS: n.s.
Darragh, 2015 [43]	50 (21.0% male, M_{age}= 22.0)	Within-subjects, counterbalanced	Placebo	VS about to-be-expected skin response to histamine after application of a (sham) antihistamine cream	1) control first, VS second 2) VS first, control second	▪ Itch levels in response to histamine skin prick following VS: ↓ at 1, 3 & 5min post histamine; n.s. at 7min ▪ Wheal response to histamine following VS: n.s.
Howe, 2017 [44]	159	Randomized controlled between-subjects	Nocebo vs. placebo	VS about either positive or negative effect of a lotion on itching; combined with either low or high experimenter warmth and competence (2x2x2 design)	1) Positive VS, high warmth, high competence 2) Positive VS, high warmth, low competence 3) Positive VS, low warmth, high competence 4) Positive VS, low warmth, low competence 5) Negative VS, high warmth, high competence 6) Negative VS, high warmth, low competence 7) Negative VS, low warmth, high competence 8) Negative VS, low warmth, low competence 9) Neutral suggestions, high warmth + competence	▪ Itch and anxiety not described ▪ Wheal and flare after positive VS compared to negative VS: ↓ ▪ Wheal and flare following positive/negative VS compared to neutral: n.s.

Supplementary Table S3 *(continued 4/8)*

Author, year	*Subjects N (sex, age)*	*Study design*	*Category / type of comparison*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Meeuwis, 2018 [45]	92 (18.5% male, M_{age}= 21.3)	Randomized controlled between-subjects	Open-label placebo	Participants were given positive verbal suggestions that a histamine test would elicit little itch. They were told that expectations play a large role in how itch is experienced, and that the suggestion provided would likely already cause them to experience little itch. A control group was given no suggestions.	1) Open-label verbal suggestions 2) Control	After suggestions: ▪ Expected itch: ↓ ▪ Self-rated itch: n.s. ▪ Self-reported skin response: marginally ↓ ▪ Physical skin response: n.s.
Peerdeman, 2015 [46]	116 (29.0% male, M_{age}= 21.8)	Randomized controlled between-subjects	Placebo	Positive VS were given with and without imagery. Participants were given an inert pill and were told that people become less sensitive to physical sensations after taking the substance. For positive imagery, people were told to imagine their best possible health.	1) VS 2) Imagery 3) VS + imagery 4) Control	▪ Expectations of pain, itch, and fatigue ↓ following VS and imagery ▪ Physical sensitivity (pain, itch, fatigue combination score): n.s. ▪ Separate scores for pain, itch, fatigue: n.s. ▪ HR, and skin conductance: n.s.
Skvortsova, 2018 [47]	108 (all female, M_{age}= 22.1)	Randomized controlled between-subjects	Placebo	Positive verbal suggestions (VS) were given about a nasal spray (2x2 design). The spray contained either oxytocin (OXY) or saline. Participants received suggestions that the spray would decrease cold-water induced pain and histamine-induced itch, or neutral instructions.	1) No VS, no OXY 2) No VS, OXY 3) VS, no OXY 4) VS, OXY	▪ Expected pain & itch ↓ following VS compared to neutral. OXY and VS x OXY effects n.s. ▪ Pain (cold pressor task) ↓ following VS. OXY and VS x OXY effects n.s. ▪ Itch in response to histamine n.s. ▪ Wheal response to histamine & skin temperature following histamine: n.s.
Van Laarhoven, 2011 [48] ***Part 1***	105 (all female, M_{age}= 21.8)	Randomized controlled between-subjects	Nocebo vs. placebo	Suggestions for either pain or itch were given about electrical (dermal) stimuli. Participants were told that 95% of people experience pain/itch from the stimuli to induce high expectations. In control conditions, it was told that very few (5%) experience pain/itch to induce low expectations.	1) itch nocebo (high expectation), 2) itch nocebo control (low expectation), 3) pain nocebo (high expectation), 4)pain nocebo control (low expectation)	▪ Mechanically, electrically and chemically induced itch ↑ in itch nocebo compared to placebo control ▪ Mechanically, electrically and chemically induced pain ↑ in pain nocebo compared to placebo control

Supplementary Table S3 *(continued 5/8)*

Author, year	*Subjects N (sex, age)*	*Study design*	*Category / type of comparison*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Van Laarhoven, 2011 [48] ***Part 2***	69 (from part 1)	Randomized controlled between-subjects	Placebo (*follows nocebo VS*)	Suggestions for low pain and itch were given about histamine iontophoresis. Participants were told that a substance was added to iontophoresis that would reduce itch / pain, so that nearly all participants would not experience itch / pain anymore. In control condition, it was told that nearly all participants experience itch / pain from the stimuli.	1) itch placebo 2) itch placebo control 3) pain placebo 4) pain placebo control	▪ Histamine induced pain & itch: effect of VS n.s.
c, By conditioning only						
No studies						
d, By a combination of verbal suggestions and conditioning						
Bartels, 2014 [49]	95 (23% male, M_{age}= 22.7 ± 3.2)	Randomized controlled between-subjects	Nocebo & placebo (*mixed presentation*)	Verbal suggestions (VS) about to-be-expected itch levels during presentation of colored lights, and conditioning of itch level (unconditioned stimulus; UCS) to differently colored lights (conditioned stimulus; CS)	1) VS + conditioning 2) VS 3) Conditioning 4) Control	Itch intensity during electric stimulation (assessed as change from baseline): ▪ Nocebo conditioning + VS: ↑ ▪ Nocebo VS: $\uparrow_{trend}$ ▪ Nocebo conditioning: n.s. ▪ Placebo conditioning + VS: ↓ ▪ Placebo VS: n.s. ▪ Placebo conditioning: n.s.
e. Social induction						
No studies						
II. Nocebo induction (regular)						
a, By verbal suggestions and hypnosis						
No studies						

Supplementary Table S3 *(continued 6/8)*

Author, year	*Subjects N (sex, age)*	*Study design*	*Category / type of comparison*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
b, By verbal suggestions only						
Stumpf, 2016 [50]	100 (50.0% male, M_{age}= 24.2)	Randomized controlled between-subjects	Nocebo	4 runs of skin prick tests were given, each with a different substance and suggestion: the substance causes 1) no itch (+ NaCl) (c-1), 2) some itch (+ histamine) (c-2), 3) enormous itch (+ histamine) (e-2), 4) enormous itch (+ NaCl) (e-1).	1) male participant, female investigator 2) male participant, male investigator 3) female participant, female investigator 4) female participant, male investigator	Whole sample: ▪ Wheal response (extent intensity) ↑ following suggestions +NaCl (difference between e1- c1) ▪ Self-rated itch & rated unpleasantness in response to skin prick tests ↑ following suggestions +NaCl (difference between e1- c1) ▪ Flare response (extent intensity) ↑ following suggestions +histamine (difference between e2 - c2) Effects of sex: ▪ Flare response ↑ for female investigators in comparison of histamine control + VS (difference between e2 - c2)
c, By conditioning only						
No studies						
d, By a combination of verbal suggestions and conditioning						
Van de Sand, 2018 [51]	30 (40.0% male, M_{age}= 25.5)	Within-subjects	Nocebo	Verbal suggestions (VS) were given that "subliminal TENS" (Transcutaneous Electrical Nerve Stimulation) aggravates pre-existing itch. Histamine was given in combination with thermal stimulation to generate a slight itch sensation. To convince participants that TENS was used, an initial conditioning procedure was conducted outside the scanner, where subjects experienced an increased itch sensation during "TENS" application. Itch was increased by increasing the amount of histamine provided under cooling conditions.	None	▪ Self-rated itch ↑ during nocebo conditions compared to control fMRI data: ▪ Contralateral (right) rolandic operculum activity ↑ during nocebo conditions compared to control ▪ Functional coupling between the insula and the periaqueductal gray (PAG) ↑ during nocebo conditions compared to control

Supplementary Table S3 *(continued 7/8)*

Author, year	*Subjects N (sex, age)*	*Study design*	*Category / type of comparison*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Bartels, 2017 [52] *Part 1*	129 (21.3% male, M_{age}= 20.3 ± 2.5)	Within-subjects	Nocebo *(as preparation to reversal)*	VS about to-be-expected itch levels during presentation of colored lights, and conditioning of itch level (UCS) to colored lights (CS)	1) Nocebo VS + conditioning	Itch intensity during electric stimulation: ▪ Nocebo conditioning + VS: ↑
Bartels, 2017 [52] *Part 2*	129 (21.3% male, M_{age}= 20.3 ± 2.5)	Randomized controlled between-subjects	Placebo *(nocebo reversal)*	VS about to-be-expected itch levels during presentation of colored lights, and counterconditioning of itch level (UCS) to colored lights (CS)	1) Nocebo VS + conditioning 2) Placebo VS + conditioning 3) Extinction	Itch intensity during electric stimulation: ▪ Placebo VS + conditioning ↓
Bartels, 2017 [52] *Part 3*	129 (21.3% male, M_{age}= 20.3 ± 2.5)	Randomized controlled between-subjects	Nocebo & placebo *(carry-over)*	VS about to-be-expected itch levels during presentation of colored lights	1) Nocebo VS + conditioning 2) Placebo VS + conditioning 3) Extinction	Itch intensity during histamine iontophoresis: Placebo VS + conditioning ↓
e. Social induction						
Holle, 2012 [53] *Experiment 1*	51 (33.3% male, M_{age}= 21.1)	Within-subjects	Social induction (contagious itch)	Short videos of people scratching on different body locations were shown and compared with neutral control videos	None	▪ Itch in response to scratching videos: ↑ Scratching in response to videos: ↑
Holle, 2012 [53] *Experiment 2 (fMRI)*	18 (out of 51 participants from experiment 1)	Within-subjects	Social induction (contagious itch)	Short videos of people scratching on different body locations were shown and compared with neutral control videos	None	Brain activation: Activation of major areas of the itch matrix, including the thalamus, primary somatosensory cortex, premotor cortex (BA6), and insula following scratching videos: ↑
Lloyd, 2012 [54]	30 (6.7% male, M_{age}= 19.3)	Within-subjects, 2x3 factorial within-groups design	Social induction (contagious itch)	Pictures were shown to evoke itch sensations and scratching. Neutral, non-itch-related pictures were shown as control. Itch-evoking images were subdivided: 1) 'skin contact', 2) 'skin response', 3) 'context'	None	▪ Main effect of picture type 'itch' compared to 'non-itch' on self-reported itch and scratching: ↑ Picture type effects: ▪ Itch-related skin-contact pictures: ↑ itch, compared to skin-response pictures and context pictures. Itch-related skin-response pictures: ↑ scratching, compared to skin-contact pictures and context pictures.

Supplementary Table S3 *(continued 8/8)*

Author, year	*Subjects N (sex, age)*	*Study design*	*Category / type of comparison*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Mitchell, 1995 [55]	63 (42.9% male)	Randomized controlled between-subjects	Nocebo	Suggestions of itch were given either subliminally or supraliminally in an audiotaped music fragment.	1) Music + subliminal suggestions of itch 2) Music only 3) Music + supraliminal suggestions of itch	Itch-associated words scored in an open-ended free-association segment & checklist-segment with itching-type sensations: ▪ reported itching ↑ in supraliminal compared to subliminal & music only groups. ▪ Scratching behavior ↑ in supraliminal vs. subliminal & music only groups.

Note. CS = conditioned stimulus; DCP = dephenylcyclopropenone; DNCB = dinitrochlorobenzene; DTH = delayed-type hypersensitivity response; HR = heart rate; HRV = heart rate variability; LA = left arm; NaCl = natriumchloride; n.s. = non-significant; OXY = oxytocin; PAG = periaqueductal gray; RA = right arm; TENS = transcutaneous electrical nerve stimulation; UCS = unconditioned stimulus; VS = verbal suggestions; VZ = varicella zoster

Supplementary Table S4. Overview of studies with patient samples.

Author, year	*Subjects N (sex, mean age)*	*Condition studied*	*Category / type of comparison*	*Study design*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
I. Placebo induction (regular)							
a. By verbal suggestions and hypnosis							
Black, 1963a [56]	12	Allergy	Placebo	Within-subjects	Verbal suggestions (VS) not to react to allergen, plus hypnosis	None	Immediate type hypersensitivity response to allergen: ▪ Skin temperature: ↓ ▪ Skinfold-thickness: ↓
Fry, 1964 [57] *Experiment 1*	47	Allergic asthma, hay fever, or pollen or dust mite allergy	Placebo	Between-subjects	VS not to react to test, plus hypnosis	1) controls (no VS, no hypnosis) 2) VS+ hypnosis	▪ Wheal size in response to allergen after VS and hypnosis: ↓ ▪ Flare size in response to allergen after VS and hypnosis: ↓
Fry, 1964 [57] *Experiment 2*	47	Allergic asthma, hay fever, or pollen or dust mite allergy	Placebo	Between-subjects	VS not to react to test, plus hypnosis	1) VS + hypnosis for one arm only 2) VS + hypnosis for both arms 3) Hypnosis, no suggestions	▪ Wheal size after VS and hypnosis: n.s. ▪ Flare after VS and hypnosis: n.s.
Hajek, 1990 [58]	13; 24 healthy controls (HC)	Atopic eczema	Placebo	Within-subjects	VS that the immune system would remove damaged cells and that the disease would be cured, plus hypnosis	1) patients with atopic eczema given suggestions 2) HC given suggestions 3) HC	▪ Cutaneous pain threshold after VS in patients and HC: ↑ ▪ Pain threshold increase correlated with improvement of atopic eczema symptoms
Laidlaw, 1994 [59]	5 (40% male, M_{age}= 22.0)	Asthma	Placebo	Within-subjects	VS of numbness, coolness, non-reactivity and dissociation were given for one arm, and of being alive and reactive for the other arm; plus hypnosis	None	▪ Flare size after positive VS compared to control sessions: ↓ ▪ Wheal sizes after positive VS compared to control sessions: n.s. ▪ Flare and wheal sizes compared to other arm within hypnosis sessions: n.s.

Supplementary Table S4 *(continued 2/10)*

Author, year	*Subjects N (sex, mean age)*	*Condition studied*	*Category / type of comparison*	*Study design*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Langewitz, 2005 [60]	79 (51.9% male)	Hay fever	Placebo	Within-subjects counterbalanced	Self-hypnosis was instructed in 2 to 5 sessions: following standard trance induction, patients were instructed to imagine a 'safe place' where breathing was undisturbed, eyes, nose and throat were feeling comfortable and cool. Patients were advised to perform self-hypnosis at the onset of allergic symptoms.	1) 1st season: learning self-hypnosis, 2nd season: continuing self-hypnosis 2) 1st season: standard anti-allergic treatment, 2nd season: learning self-hypnosis	▪ Daily self-reported symptoms and medication use in season 1 following self-hypnosis, compared to standard treatment: n.s. ▪ Retrospective symptoms following self-hypnosis: ↓ ▪ Nasal flow symptoms in season 1 following self-hypnosis compared to control: n.s. ▪ Symptoms reported during nasal flow test following self-hypnosis compared to baseline: ↓ ▪ Time to reach critical dose following self-hypnosis compared to baseline: ↑
Levine, 1966 [61]	Group 1: 10 (70.0% male) Group 2: 10 (20.0% male) Group 3: 10 (40.0% male)	Group 1: allergic or sensitive to ragweed Group 2: urticaria Group 3: healthy controls (HC)	Nocebo vs. placebo	Within-subjects	HC were instructed that the skin tests on one arm would react more compared to previous (baseline) visit, and that the other arm would react less. In patient groups, the instruction was given that one arm would react less and the other the same as previous. Given under hypnosis.	None	▪ Response to histamine after hypnosis and VS (assessed by wheal and flare size to histamine and phosphate dilutions): n.s.
Schertzer, 1987 [62]	15 (26.7% male)	Chronic urticaria	Placebo	Within-subjects, counterbalanced	Participants received two sessions: 1) hypnotic induction and suggestions for symptom relief; and 2) a control session. Suggestions for skin clearing and disappearance of hives were given.	None	Self-rated itch following hypnosis treatment: ↓ ▪ Number of wheals following hypnosis treatment: n.s.

Supplementary Table S4 *(continued 3/10)*

Author, year	*Subjects N (sex, mean age)*	*Condition studied*	*Category / type of comparison*	*Study design*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Sinclair-Gieben, 1959 [63]	14	Bilateral and multiple common warts	Placebo	Within-subjects	Suggestions were given that the warts on one side (usually hand) would disappear (other side of the body was control), with hypnosis.	None	▪ Any immediate improvement in number of warts observed was on the treated side.
Surman, 1973 [64]	36	Bilateral warts of common or planar type	Placebo	Between-subjects (comparison with untreated controls)	Suggestions were given that a tingling sensation in the warts on one side of the body (chosen by the patient) would be experienced and that only those warts would subsequently disappear. Suggestions were given with hypnosis.	1) experimental 2) untreated control	▪ Nine patients (53%) experienced improvement in warts following treatment; 0% in untreated controls [A]
Tausk, 1999 [65]	11	Psoriasis	Placebo	Between-subjects	Active suggestions under hypnosis or neutral hypnosis were given. Suggestions were that patients' psoriasis would improve, neutral consisted of suggestions of relaxation and wellbeing inherent to the hypnosis procedure.	1) Active suggestions 2) neutral	▪ Clinical psoriasis severity (PASI) following active suggestions: n.s. *Greater improvement found in highly hypnotizable individuals.*
Ullman, 1960 [66]	15 (good hypnotizable patients) *+ 47 poorly hypnotizable controls*	Multiple vulgar warts (n=9), both multiple vulgar warts and plantar warts (n=4), single vulgar wart (n=1), multiple condyloma acuminate (n=1) *Controls: multiple warts*	Placebo	Within-between-subjects (comparison between good and poorly hypnotizables)	A positive suggestion that the treatment would be successful and that the warts would begin to disappear was given, with hypnosis. The procedure was repeated on subsequent visits if little or no change in the warts was observed.	1) Good hypnotizable 2) Poorly hypnotizable	▪ A significantly higher number of cures for warts was associated with deep hypnosis than with being poorly hypnotizable

Supplementary Table S4 *(continued 4/10)*

Author, year	*Subjects N (sex, mean age)*	*Condition studied*	*Category / type of comparison*	*Study design*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
West, 1961 [67]	14	Widespread atopic dermatitis	Placebo	Within-subjects	Patients were told under hypnosis their skin was well and would react normally to the tests. The expected normal reactions were described to them as tests were performed.	None	▪ Three (21%) of the 14 patients had no delayed blanch during hypnosis. [A] ▪ Three of the 4, or 75%, who previously had not shown histamine flares, had a definite flare when tested during hypnosis [A] ▪ All 14 patients had a white line response instead of the normal red line as a result of stroking the skin before, during, and after hypnosis [A]
b. By verbal suggestions only							
Schaefer, 2016 [68]	25 (16.0% male, M_{age}= 26.0)	Allergic rhinitis	Open-label (OL) placebo	Randomized controlled, between-subjects	Participants received an explanation about placebos and placebo effects, and were asked to take inert pills twice daily for 14 days.	1) OL placebo + treatment as usual (TAU) 2) TAU only	▪ Allergic symptoms composite score following open-label placebos + TAU ↓ compared to TAU only ▪ Separate allergic symptoms n.s.
Schaefer, 2018 [69]	46 (19.6% male, M_{age}= 24.9)	Allergic rhinitis	Open-label (OL) placebo	Randomized controlled, between-subjects	A 2x2 design was used in which participants were asked to take inert pills twice daily for 14 days or received no inert pills (with and without information on placebo effects) . All patients used medication (treatment as usual, TAU).	1) OL placebos with briefing + TAU 2) OL placebos w/o briefing + TAU 3) TAU with briefing 4) TAU w/o briefing	▪ Allergic symptoms composite score ↓ over time for OL placebos + TAU compared to TAU only. ▪ Briefing effects on symptoms n.s.
c, By conditioning / conditioned dose reduction							
Ader, 2010 [70]	46 (46% male)	Psoriasis	Placebo	Randomized controlled between-subjects	Conditioned dose reduction with partial reinforcement	1) standard therapy 2) partial reinforcement 3) dose control	▪ Psoriasis severity scale (PSS) during partial reinforcement vs. control and standard therapy: ↓ in 1 of 2 sites ▪ Relapse in psoriasis during partial reinforcement vs. control and standard therapy: ↓

Supplementary Table S4 *(continued 5/10)*

Author, year	*Subjects N (sex, mean age)*	*Condition studied*	*Category / type of comparison*	*Study design*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Goebel, 2008 [71]	30 (46.7% male, M_{age}= 41.1)	Monovalent allergy to dust mite	Placebo	Randomized controlled between-subjects	Conditioning of antihistamine effects (UCS) to a green-colored milkshake (CS)	1) conditioned-not-evoked (water + placebo) 2) conditioned (drink + placebo) 3) drug (water + desloratadine)	Subjective allergic symptoms: n.s. between groups Wheal size in response to dust mite: n.s. between groups Basophil activation: ↓ in conditioned and drug group vs. conditioned-not-evoked Blood count & flow cytometry: n.s. between groups
Vits, 2013 [72]	63 (39.7% male, M_{age}= 30.3)	Dust mite allergy	Placebo	Randomized controlled between-subjects	Conditioning of antihistamine effects (UCS) to a green-colored milkshake (CS)	1) conditioned 2) sham-conditioned control 3) natural history (NH)	Subjective allergic symptoms in response to nasal provocation test (NPT) ↓ in both conditioned and sham-conditioned compared to NH on 1st and 5th evocation Wheal size in response to dust mite ↓ in both conditioned and sham-conditioned compared to NH on 1st evocation, 5th evocation n.s.
d, By a combination of verbal suggestions and conditioning							
Klinger, 2007 [73]	48 (50.0% male, M_{age}= 27.4) *+ 48 matched healthy controls (HC) that were matched on age and gender*	Atopic dermatitis (AD)	Placebo	Randomized controlled, between-subjects	Conditioning of pain level (UCS) to a stimulus (ointment; CS); with or without positive verbal suggestions (VS) regarding this ointment.	1) AD, no VS, no conditioning 2) AD, no VS, conditioning 3) AD, VS, no conditioning 4) AD, VS, conditioning 5) HC, no VS, no conditioning 6) HC, no VS, conditioning 7) HC, VS, no conditioning 8) HC, VS, conditioning	Main effect of VS on pain (in response to electrical stimulation): ↓ Main effect of conditioning on pain: n.s. VS x conditioning effect on pain: ↓ No differences between HC and AD groups

Supplementary Table S4 *(continued 6/10)*

Author, year	*Subjects N (sex, mean age)*	*Condition studied*	*Category / type of comparison*	*Study design*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
e. By social induction							
Kamenica, 2013 [74]	340 (37.8% male, M_{age}= 27.7)		Social induction (effects of advertisement)	Randomized controlled between-subjects	A movie was shown to participants, which was interrupted every 5 min with advertisements for antihistamine (ah-)A (the antihistamine used in the study) and for ah-B. The advertisement of ah-B claimed that it works faster than ah-A.	1) Allergic, ah-A advertisement 2) Non-allergic, ah-A advertisement 3) Allergic, ah-B advertisement 4) Non-allergic, ah-B advertisement	Wheal size in non-allergic participants: n.s. at 60 min; ↑ efficacy following ah-A ad. at 120 min, compared to ah-B ad. Wheal size in allergic participants: ↓ efficacy following ah-A ad. at 60 min compared to ah-B ad., n.s. at 120 min.
II. Nocebo induction (regular)							
a, By verbal suggestions and hypnosis							
Hajek, 1992 [75]	8 (M_{age}= 26.4); 6 HC	Atopic eczema	Nocebo	Within-subjects	Verbal suggestions (VS) that pain is experienced in the middle of the upper part of the back, plus hypnosis	1) patients with atopic eczema 2) healthy controls	▪ Skin temperature for patients and HC: ↑ following VS
b. By verbal suggestions only							
Luparello, 1968 [76]	Group 1: 40 (35.0% male, M_{age}= 25.8) Group 2: 15 Group 3: 15 Group 4: 10	Group 1: Asthma due to allergens or irritants Group 2: Sarcoid or tuberculosis (controls) Group 3: Chronic bronchitis (controls) Group 4: healthy controls (HC)	Nocebo *(plus placebo given as nocebo reversal)*	Within-subjects	Participants were told that they would be inhaling five different concentrations of an irritant or allergen which they had previously indicted as being associated with his asthmatic attacks (in progressively increasing amounts). When dyspnea or wheezing was experienced, the inhalations were stopped and a placebo in the form of nebulized physiologic saline solution was administered; participants were told that they were receiving a bronchodilator.	None	<u>After negative suggestions:</u> ▪ conductance—thoracic gas volume ratio (Ga/TGV) ↓ compared to baseline (in 30% of subjects) ▪ Airway resistance (Ra) ↑ compared to baseline (in 30% of subjects) <u>After placebo administration with positive suggestions:</u> ▪ Ga/TGV ↑ compared to measurement after negative suggestions ▪ Ra ↓ compared to measurement after negative suggestions

Supplementary Table S4 *(continued 7/10)*

Author, year	*Subjects N (sex, mean age)*	*Condition studied*	*Category / type of comparison*	*Study design*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
McFadden, 1969 [77]	29 (34.5% male)	Bronchial asthma	Nocebo *(plus placebo given as nocebo reversal)*	Within-subjects	Each subject was informed that they would be inhaling five concentrations of an irritant or allergen that they associated with their asthma attacks. In the event that dyspnea and wheezing occurred, a placebo in the form of nebulized saline was administered. The subjects were told that they were receiving a bronchodilator. Testing was conducted twice, on separate days.	None	<u>After negative suggestions on day 1 & 2 both:</u> ▪ Conductance—thoracic gas volume ratio (Ga/TGV) ↓ compared to baseline for reactors (51.7%) ▪ Airway resistance (Ra) ↑ compared to baseline for reactors (51.7%) <u>After positive suggestions:</u> ▪ Ga/TGV ↑ compared to measurement after negative suggestions ▪ Ra & TGV ↓ compared to measurement after negative suggestions <u>When bronchodilator given as allergen:</u> ▪ Ga/TGV ↑ in nonreactors. In reactors, Ga/TGV n.s.
Napadow, 2015 [78]	14 (57.1% male, M_{age}= 25.4)	Atopic dermatitis	Nocebo	Within-subjects, counterbalanced	Temperature-modulation fMRI scans were given. A clear, odorless saline solution was pricked into the forearm. For the 'open' saline control run, the solution was a 'simple drop of water, which we are using as a control condition to compare with the drop of allergen you will receive later'. For the 'nocebo' saline fMRI run, subjects were led to expect an allergen solution prick test at this scan, as experienced previously.	None	▪ Itch ↑ in nocebo condition compared to open saline ▪ Expected itch correlated with self-reported itch. <u>fMRI data:</u> ▪ fMRI signal increase during the increasing itch phase in the dorsolateral prefrontal cortex (dlPFC), caudate, and intraparietal sulcus (iPS): ↑ compared to open saline
Weiss, 1970 [79]	16 (62.5% male)	Allergic asthma	Nocebo	Within-subjects	Suggestions were given that patients would be given a bronchial challenge test using a substance to which they were known to be allergic It was told that five inhalations of each of several strengths of extract were given, starting with a highly dilute extract and continuing through higher concentrations (max. 6) until wheezing was experienced. Control (saline) inhalations would be given as well.	None	Suggestion had no significant effects on any of the included measures (Wright-McKerrow Peak Flow meter; maximum expiratory flow rate; respiratory pattern)

Supplementary Table S4 *(continued 8/10)*

Author, year	*Subjects N (sex, mean age)*	*Condition studied*	*Category / type of comparison*	*Study design*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
c, By conditioning only							
Barrett, 2000 [80] *experiment 1*	60	Seasonal allergic rhinitis	Nocebo	Randomized controlled between-subjects	Conditioning paradigm with single acquisition and 2 evocations	1) Placebo control (No CS, PLA) 2) CS control (CS, PLA) 3) Experimental (CS, UCS -> CS, PLA) 4) UCS control (No CS, UCS -> No CS, PLA)	▪ Subjective symptoms scores (SSS) n.s. between groups ▪ peak nasal inspiratory flow (PNIF) ↑ in conditioned groups on 1st evoc ▪ Histamine levels ↑ in conditioned groups
Barrett, 2000 [80] *experiment 2*	15 (conditionable participants of exp. 1)	Seasonal allergic rhinitis	Nocebo	Randomized controlled between-subjects	Conditioning paradigm with 1, 2, or 3 acquisitions and 2 evocations	1) 1 acq trial group 2) 2 acq trials group 3) 3 acq trials group	▪ SSS n.s. between groups ▪ PNIF n.s. between groups ▪ Histamine levels: ↑ on 1st evoc in 3 acq. group exclusively
Booth, 1995 [81]	15 (33.3% male, M_{age}= 21.1)	Allergic to dust mite, gras pollen, animals	Nocebo	Within-subjects	Conditioning paradigm with 8 acquisitions and 2 evocations	None	▪ Wheal size to sham allergen compared to real allergen response: n.s.
Gauci, 1994 [82]	22 (22.7% male)	Allergic to dust mite	Nocebo	Randomized controlled between-subjects	Conditioning of an allergic response to dust mite (UCS) to a blue colored drink (CS)	1) Conditioned group 2) CS control group 3) UCS control group	▪ Subjective allergic symptoms after conditioning: n.s. ▪ Nasal tryptase level after conditioning: ↑
Jordan, 1972 [83]	18 (33.3% male, M_{age}= 25.3) *+ 18 matched controls with non-dermatological medical conditions*	Atopic dermatitis (AD)	Nocebo	Within-subjects	Conditioning of an itch stimulus (UCS) with a modified bell of constant loudness (CS), with 75% intermittent reinforcement	1) AD patients 2) Other non-dermatology (control) patients	Effects on itch (as measured by scratching; patients were instructed to scratch lightly when an itch stimulus was perceived) and on galvanic skin response (GSR): ▪ No. of trials to habituate to CS: ↑ in AD ▪ No. of conditioned scratch & GSR responses: ↑ ▪ in AD

Supplementary Table S4 *(continued 9/10)*

Author, year	*Subjects N (sex, mean age)*	*Condition studied*	*Category / type of comparison*	*Study design*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Robertson, 1975 [84]	11 (45.5% male, M_{age}= 50.5) *+ 11 matched controls*	Lichen simplex *Controls were treated for: solar keratoses (n=8), tinea cruris (healing, n=1), pityriasis rosea (healed, n=1), chronic psoriasis (n=1)*	Nocebo	Within-subjects *Effects were compared across patients and HC*	Scratch responses were conditioned; an electrical itch stimulus (UCS) was paired with a tone (CS). Patients were instructed to scratch if they experienced itch.	None	▪ No. of conditioned scratch responses in lichen simplex compared to controls: ↑
d, By a combination of verbal suggestions and conditioning							
No studies							
d, By social induction							
Niemeier, 2000 [85]	14 (M_{age}= 36.4) *+ 11 (M_{age}= 43.1) who stated to be free of skin diseases*	Skin disease	Nocebo (contagious itch)	Within-subjects ABA design	A public lecture was organized: 'Itching – what's behind it?'. The first part of the lecture included slides that induce itching (pictures of fleas, mites, scratch marks on the skin, allergic reactions etc.), while the second part showed slides that induce relaxation and sense of well-being.	None	In both participants with and without skin disease: ▪ itch ↑ when itch slides were presented compared to relaxation part. ▪ scratching ↑ when itch slides were presented compared to relaxation part.
Papoiu, 2011 [86]	11 (27.3% male, M_{age}= 32.7) *+ 14 healthy volunteers (57.1% male, M_{age}=27.1)*	Mild to moderate atopic dermatitis (AD)	Nocebo *(visual transmission of itch)*	Within-subjects	Participants watched short 5 min clips of people scratching their forearm, or of neutral content as control. The order of videos was randomized. Participants received either a mock or itch stimulus during the video (iontophoresis with either an isotonic aqueous (saline) solution or 1% histamine dihydrochloride).	None	▪ In AD: itch ↑ for itch video + itch stimulus compared to neutral video + itch stimulus. ▪ In healthy: itch n.s. ▪ Atopics and in AD: scratching behaviour ↑ for itch video+saline and itch video+itch stimulus.

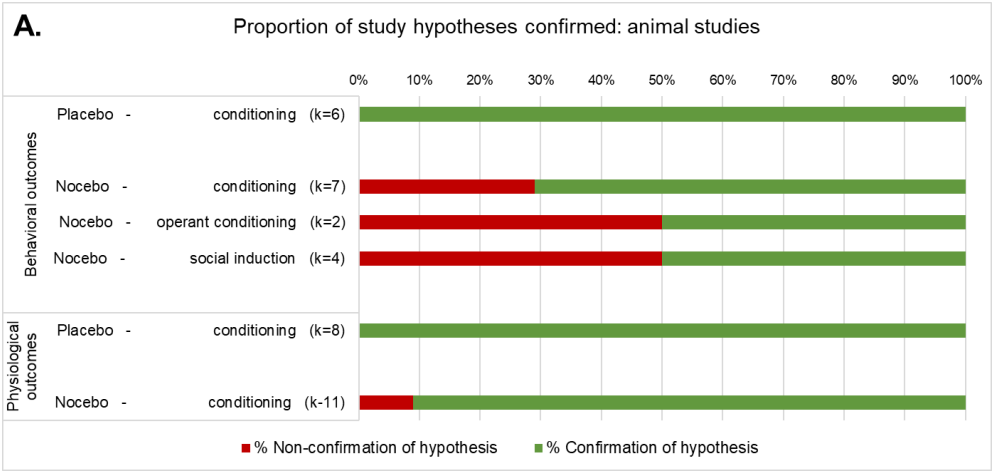
Supplementary Table S4 *(continued 10/10)*

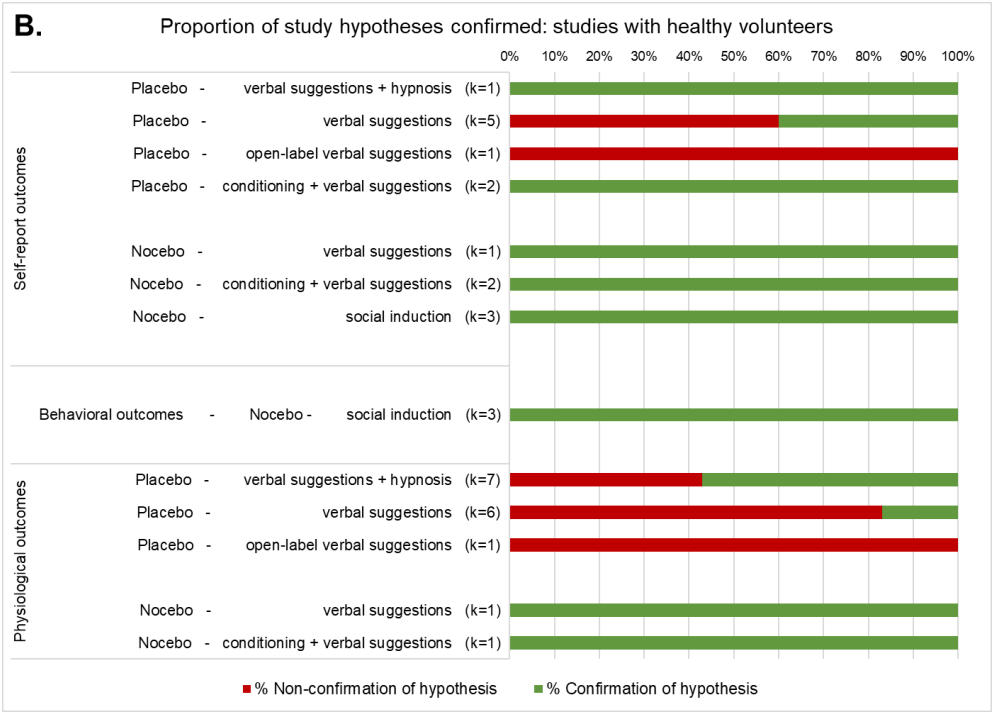
Author, year	*Subjects N (sex, mean age)*	*Condition studied*	*Category*	*Study design*	*Induction method type*	*Experimental conditions*	*Short summary of study findings*
Schut, 2014 [87]	27 (44.4% male, M_{age}= 23.6) *+ 28 healthy volunteers (35.7% male, M_{age}= 23.3)*	Atopic dermatitis	Nocebo (contagious itch)	Within-between-subjects (comparison between patients and controls)	Itch-inducing and neutral videos were presented (order was counterbalanced). An experimental video (EV) on "Itch – what is behind it?" was used to induce itch, while a video on "Skin – the communication organ" served as a control video (CV). Pictures were selected according to a former study (Niemeier, 2000)	None	▪ Self-rated itch ↑ after EV compared to CV ▪ Number of scratch movements ↑ after EV compared to CV
Schut, 2017 [88]	11 (45.5% male, M_{age}= 32.8) *Participants were selected on being responsive to visual itch cues*	Atopic dermatitis	Nocebo (contagious itch)	Within-subjects, counterbalanced	Itch was induced by a video showing people scratching (EV). A video showing the same people sitting idle was used as a control (CV).	None	Self-rated itch ↑ after EV compared to CV Number of scratch movements ↑ after EV compared to CV <u>fMRI data:</u> SMA, the left ventral striatum and the right OFC activation ↑ after EV compared to CV.
Von Leupoldt, 2012 [89]	19 (26.3% male, M_{age}= 32.2) *+ 19 matched healthy controls (31.6% male, M_{age}= 31.7)*	Allergic asthma	Nocebo (visually induced)	Within-between-subjects	2 series of 30 pictures were shown. The Allergy series depicted house dust, cat fur, and various plants with their pollens. The Neutral series depicted emotionally neutral scenes (e.g., household objects and neutral faces).	1) Allergic asthma 2) HC	Allergic symptoms ↑ for Neutral to Allergy series in patients compared to HC <u>Respiratory parameters:</u> Breathing frequency ↑ for Neutral to Allergy series in patients compared to HC. Other respiratory parameters (airflow, V'; tidal volume, VT; inspiratory time, TI; and respiratory resistance, ROS) n.s.

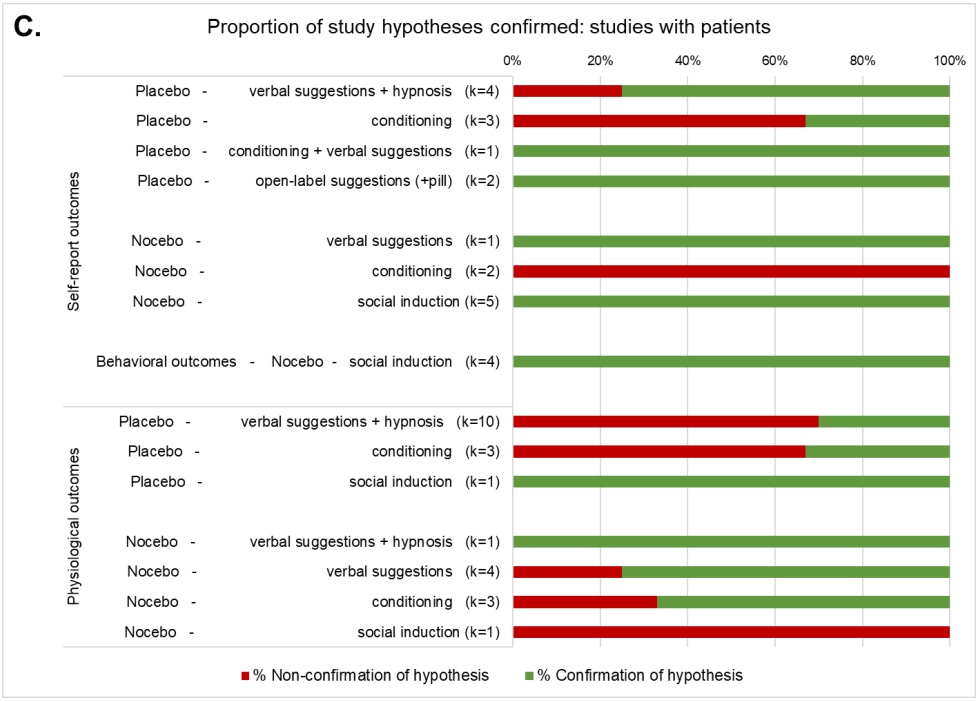
Note. acq = acquisition; AD = atopic dermatitis; ad. = advertisement; ah = antihistamine; CS = conditioned stimulus; CV = control video; dlPFC = dorsolateral prefrontal cortex; EV = experimental video; evoc = evocation; Ga/TGV = conductance—thoracic gas volume ratio; GSR = galvanic skin response; HC = healthy controls; iPS = intraparietal sulcus; NH = natural history; NPT = nasal provocation test; n.s. = non-significant; OL = open label; PLA = placebo; PNIF = peak nasal inspiratory flow; PSS = psoriasis severity scale; Ra = airway resistance; ROS = respiratory resistance; SSS = subjective symptom scores; TAU = treatment as usual; TI = inspiratory time; UCS = unconditioned stimulus; V' = airflow; VS = verbal suggestions; VT = tidal volume.

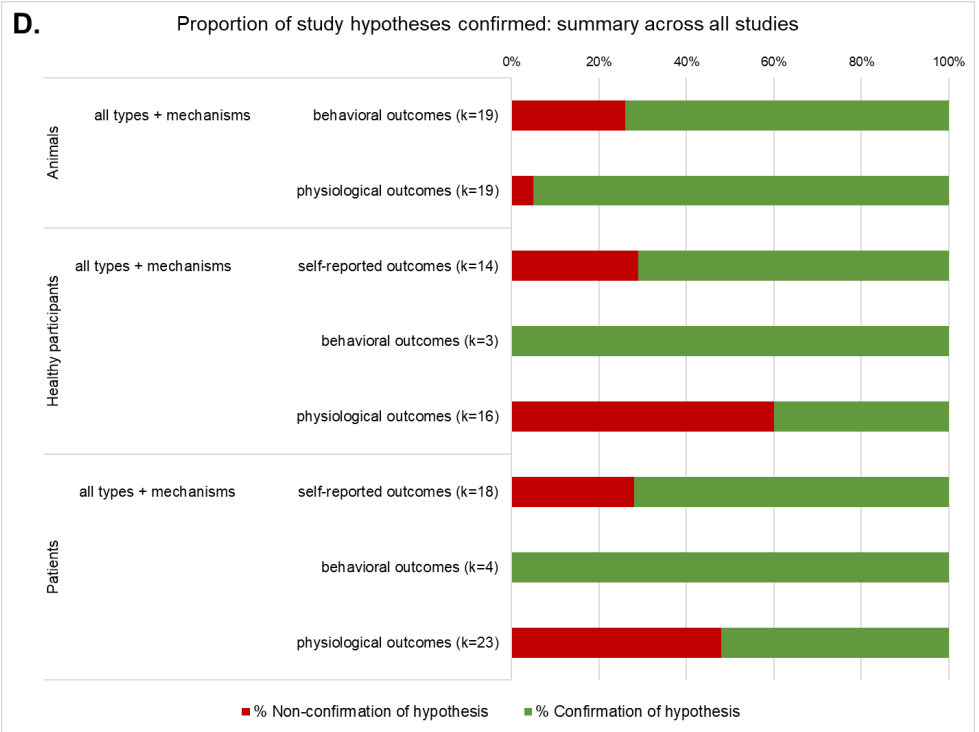
[A] Studies did not indicate statistical significance of findings. As such, percentages are given in this table.

Supplementary Figure S1. Proportion of hypotheses confirmed by different placebo and nocebo effect induction methods for (A) animals studies, (B) studies with healthy volunteers, and (C) studies with patients, with a summary of results presented in (D). Percentages were derived from the results described in Supplementary Table S1.

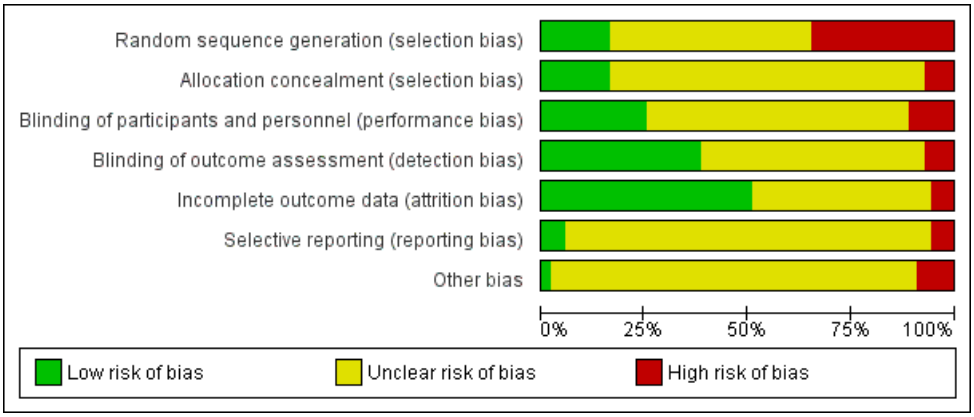




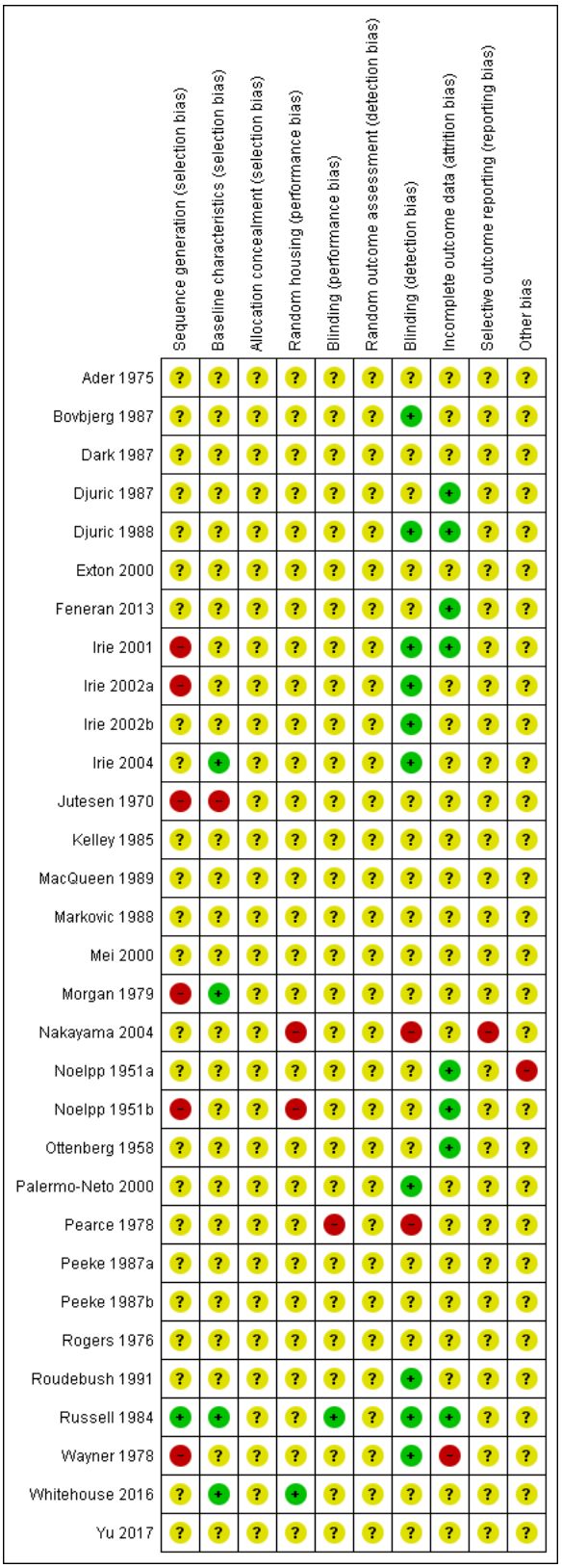

C.
Proportion of study hypotheses confirmed: studies with patients
0%
20%
40%
60%
80%
100%
Self-report outcomes
Placebo - verbal suggestions + hypnosis (k=4)
Placebo - conditioning (k=3)
Placebo - conditioning + verbal suggestions (k=1)
Placebo - open-label suggestions (+pill) (k=2)
Nocebo - verbal suggestions (k=1)
Nocebo - conditioning (k=2)
Nocebo - social induction (k=5)
Behavioral outcomes - Nocebo - social induction (k=4)
Physiological outcomes
Placebo - verbal suggestions + hypnosis (k=10)
Placebo - conditioning (k=3)
Placebo - social induction (k=1)
Nocebo - verbal suggestions + hypnosis (k=1)
Nocebo - verbal suggestions (k=4)
Nocebo - conditioning (k=3)
Nocebo - social induction (k=1)
% Non-confirmation of hypothesis
% Confirmation of hypothesis


D.
Proportion of study hypotheses confirmed: summary across all studies
0%
20%
40%
60%
80%
100%
Animals
all types + mechanisms
behavioral outcomes (k=19)
physiological outcomes (k=19)
Healthy participants
all types + mechanisms
self-reported outcomes (k=14)
behavioral outcomes (k=3)
physiological outcomes (k=16)
Patients
all types + mechanisms
self-reported outcomes (k=18)
behavioral outcomes (k=4)
physiological outcomes (k=23)
% Non-confirmation of hypothesis
% Confirmation of hypothesis

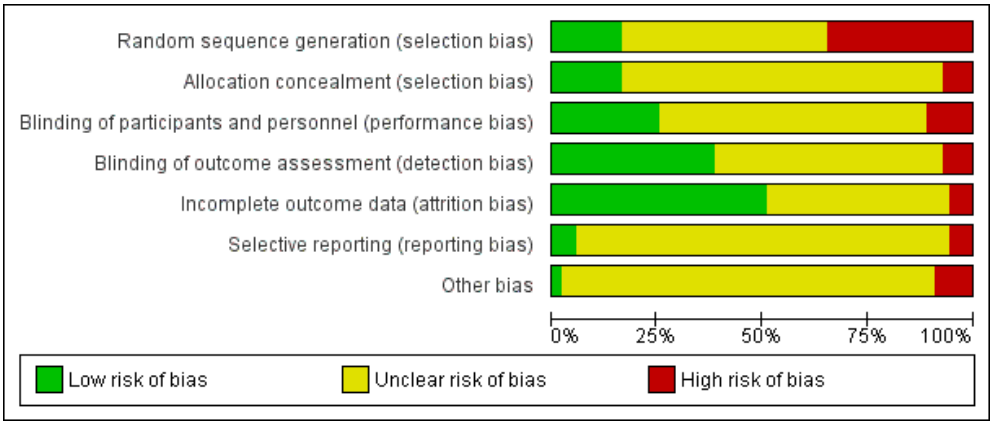
Supplementary Figure S2. General summary of the results for the Risk of Bias analysis for animal trials.



Supplementary Figure S3. Overview of the Risk of Bias for each article: animal trials.



Supplementary Figure S4. General summary of the results for the Risk of Bias analysis for human trials.



Supplementary Figure S5. Overview of the Risk of Bias for each article: human trials

Supplementary Figure S6. Search strategies for PubMed, Embase, and PsycInfo databases

PubMed search

(„nocebo“ [tiab] OR „inert“ [tiab] OR “sham” [tiab] OR “dummy” [tiab] OR “aversive conditioning” [tiab] OR “configural learning” [tiab] OR “associative learning” [tiab] OR “mediated learning” [tiab] OR “animal learning” [tiab] OR “verbal reinforcement” [tiab] OR “attribution” [tiab] OR “conditioning” [tiab] OR “pavlov*” [tiab] OR “expecta*” [tiab] OR “expectation*” [tiab] OR “social learning” [tiab] OR “suggestibility” [tiab] OR “placebo response*” [tiab] OR “placebo effect*” [tiab] OR “placebo induced” [tiab] OR “suggestion*” [tiab] OR “placebo effect” [mesh] OR “nocebo effect” [mesh] OR “conditioning (psychology)” [mesh] OR “association learning” [mesh] OR “anticipatory learning” [tiab] OR “contagious” [tiab]) AND (“quantitative sensory testing” [tiab] OR “QST” [tiab] OR “histamin*” [tiab] OR “capsaicin” [tiab] OR “cowhage” [tiab] OR “cowage” [tiab] OR “scratch*” [tiab] OR “rash” [tiab] OR “pruri*” [tiab] OR “Pruritus” [tiab] OR “Pruritic” [tiab] OR “Prurigo” [tiab] OR “itch*” [tiab] OR “wheal*” [tiab] OR “weal*” [tiab] OR “extravasation” [tiab] OR “flare” [tiab] OR “neurogenic inflammation” [tiab] OR “skin” [tiab] OR “cutaneous” [tiab] OR “inflamm*” [tiab] OR “allerg*” [tiab] OR “hypersens*” [tiab] OR “anaphyla*” [tiab] OR “antigenic” [tiab] OR “pruritus” [mesh] OR “psoriasis” [tiab] OR “dermatitis” [tiab] OR “eczema” [tiab] OR “lichen planus” [tiab] OR “prurigo nodularis” [tiab] OR “neurodermatitis” [tiab] OR “lichen simplex chronicus” [tiab] OR “neurofibroma*” [tiab])

Embase search

((nocebo OR inert OR sham OR dummy OR aversive conditioning OR configural learning OR associative learning OR mediated learning OR animal learning OR verbal reinforcement OR attribution OR conditioning OR pavlov* OR expecta* OR expectation* OR social learning OR suggestibility OR placebo response* OR placebo effect* OR placebo-induced OR suggestion* OR anticipatory learning OR contagious).ti,ab. OR (placebo effect OR nocebo effect OR conditioning psychology OR association learning).sh.) AND ((quantitative sensory testing OR QST OR histamin* OR capsaicin OR cowhage OR cowage).ti,ab. OR (Scratch* OR Rash OR Pruri* OR pruritus OR prurigo OR pruritic OR Itch* OR Wheal* OR Weal* OR Extravasation OR Flare OR neurogenic inflammation OR Skin OR Cutaneous Inflamm* OR Allerg* OR Hypersens* OR Anaphyla* OR Antigenic OR psoriasis OR dermatitis OR eczema OR lichen planus OR prurigo nodularis OR neurodermitis OR lichen simplex chronicus OR neurofibroma*).ti,ab. OR (Pruritus).sh.)

PsycInfo search

((TI nocebo) OR (TI inert) OR (TI sham) OR (TI dummy) OR (TI “aversive conditioning”) OR (TI “configural learning”) OR (TI “associative learning”) OR (TI “mediated learning”) OR (TI “animal learning”) OR (TI “verbal reinforcement”) OR (TI attribution) OR (TI conditioning) OR (TI pavlov*) OR (TI expecta*) OR (TI expectation*) OR (TI “social learning”) OR (TI suggestibility) OR (TI “placebo response*) OR (TI “placebo effect*) OR (TI “placebo-induced”) OR (TI suggestion*) OR (MA “placebo effect”) OR (MA “nocebo effect” OR (MA “conditioning (psychology)” OR (MA “association learning”)) OR ((AB nocebo) OR (AB inert) OR (AB sham) OR (AB dummy) OR (AB “aversive conditioning”) OR (AB “configural learning”) OR (AB “associative learning”) OR (AB “mediated learning”) OR AB “animal learning”) OR (AB “verbal reinforcement”) OR (AB attribution) OR (AB conditioning) OR (AB pavlov*) OR (AB expecta*) OR (AB expectation*) OR (AB “social learning”) OR (AB suggestibility) OR (AB “placebo response*) OR (AB “placebo effect*) OR (AB “placebo-induced”) OR (AB suggestion*) OR (TI anticipatory learning) OR (TI contagious) OR (AB anticipatory learning) OR (AB contagious))

AND

((TI “quantitative sensory testing”) OR (TI QST) OR (TI histamin*) OR (TI “capsaicin”) OR (TI “cowhage”) OR (TI “cowage”)) OR ((AB “quantitative sensory testing”) OR (AB QST) OR (AB histamin*) OR (AB “capsaicin”) OR (AB “cowhage”) OR (AB “cowage”)) OR ((TI Scratch*) OR (TI Rash) OR (TI Pruri*) OR (TI Pruritus) OR (TI pruritic) OR (TI prurigo) OR (TI Itch*) OR (TI Wheal*) OR (TI Weal*) OR (TI Extravasation) OR (TI Flare) OR (TI “neurogenic inflammation”) OR (TI Skin) OR (TI “Cutaneous Inflamm*”) OR (TI Allerg*) OR (TI Hypersens*) OR (TI Anaphyla*) OR (MA “Antigenic Pruritus”)) OR ((AB Scratch*) OR (AB Rash) OR (AB Pruri*) OR (AB Pruritus) OR (AB pruritic) OR (AB prurigo) OR (AB Itch*) OR (AB Wheal*) OR (AB Weal*) OR (AB Extravasation) OR (AB Flare) OR (AB “neurogenic inflammation”) OR (AB Skin) OR (AB “Cutaneous Inflamm*”) OR (AB Allerg*) OR (AB Hypersens*) OR (AB Anaphyla*) OR (TI psoriasis) OR (TI dermatitis) OR (TI eczema) OR (TI lichen planus) OR (TI prurigo nodularis) OR (TI neurodermatitis) OR (TI lichen simplex chronicus) OR (TI neurofibroma*) OR (AB psoriasis) OR (AB dermatitis) OR (AB eczema) OR (AB lichen planus) OR (AB prurigo nodularis) OR (AB neurodermatitis) OR (AB lichen simplex chronicus) OR (AB neurofibroma*))

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