Placebo and nocebo effects for itch and itch-related immune outcomes: A systematic review of animal and human studies

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ARTICLE INFO

ABSTRACT

Placebo and nocebo effects can influence somatic symptoms such as pain. For itch and other dermatological symptoms these effects have been far less investigated. This review systematically integrates evidence from both animal (mainly rodents) and human trials on placebo and nocebo effects in itch, itch-related symptoms and conditions of the skin and mucous membranes, and related immune outcomes (e.g., histamine). Thirty-one animal studies, and fifty-five human studies (k = 21 healthy participants, k = 34 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 high heterogeneity across studies. Effects of suggestions were found consistently across subjective and behavioral parameters (e.g., itch and scratching in humans), whereas conditioning was likely to impact physiological parameters under certain conditions (e.g., conditioning of histamine levels in stressed rodents). Brain areas responsible for itch processing were associated with nocebo effects. Future research may investigate how variations in methods impact placebo and nocebo effects, and whether all symptoms and conditions can be influenced equally.

1. Introduction

Placebo and nocebo effects are known to influence symptom severity and treatment efficacy in various medical symptoms and conditions (Benedetti, 2014; Chavarria et al., 2017; Price et al., 2008; Wolters et al., 2019). 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 (Evers et al., 2018; Tausk et al., 2013). Nocebo effects are adverse treatment outcomes (e.g., increased side effects, reduced treatment efficacy) elicited by non-active treatment components (Evers et al., 2018). 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) (Bartels et al., 2016; Peerdeman et al., 2016; Tausk et al., 2013). In addition, some work suggests that placebo effects may still occur when it is known that a placebo is given (open-label placebo) (Carvalho et al., 2016; Charlesworth et al., 2017; Kaptchuk et al., 2010; Kelley et al., 2012; Sandler and Bodfish, 2008).

Placebo and nocebo effects have been found to impact various somatic symptoms such as pain and itch (Wolters et al., 2019). Itch is a key symptom of many dermatological conditions (Leslie, 2013; Yosipovitch and Samuel, 2008), has a high impact on patients' quality of life and has high economic costs (Silverberg et al., 2016; Steinke et al., 2018; Tripathi et al., 2019). 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 % (Weisshaar et al., 2019). 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 (Dong and Dong, 2018). A meta-analysis shows that at least 30 percent of itch reduction in randomized controlled trials can be explained by placebo effects (van Laarhoven et al., 2015). 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 (Benedetti et al., 2018; Geuter et al., 2017).

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 (Stumpf et al., 2016). Literature moreover shows that conditioning can influence immune parameters in animal models and human populations (Hadamitzky et al., 2018; Skvortsova et al., 2019; Tekampe et al., 2017). 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 (Bartels et al., 2016; Peerdeman et al., 2016; Wolters et al., 2019), 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.

2. 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 (Moher et al., 2009) 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 (Higgins et al., 2011). The SYRCLE risk of bias tool was used for articles
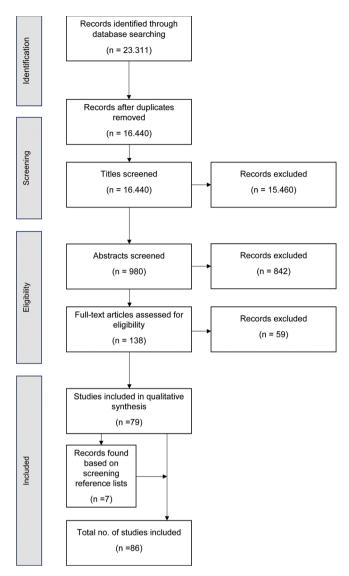

Fig. 1. Flowchart for the selection of articles to be included in the systematic review.

describing animal research (Hooijmans et al., 2014), as were the guidelines described by O'Connor and Sargeant (2014).

3. Results

3.1. 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 Fig. 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 Fig. 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

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 (Ader and Cohen, 1975; Exton et al., 2000; Kelley et al., 1985; Rogers et al., 1976; Roudebush and Bryant, 1991; Wayner et al., 1978)	–
			Physiological	DTH response to SRBC: hemagglutination titers (Ader and Cohen, 1975; Rogers et al., 1976; Wayner et al., 1978), paw swelling (Bovbjerg et al., 1987), footpad swelling (Kelley et al., 1985), plasma glucocorticoids (Kelley et al., 1985), DNCB-induced ear swelling (Exton et al., 2000), left/right ear weight ratio (Mei et al., 2000), leukocyte migration inhibitory factor (Mei et al., 2000) Sensitization to corticosterone: DTH-induced paw swelling (Roudebush and Bryant, 1991)	–
	Nocebo	Conditioned allergic responses and anaphylactic shock	Behavioral	Saccharin preference ratio (Djurić et al., 1987, 1988; Marković et al., 1988), anaphylactic shock behavior (Djurić et al., 1987, 1988), breathing pattern indicative of asthmatic attack (Noelpp and Noelpp-Eschenhagen, 1951b), asthma attack (Ottenberg et al., 1958), lung anaphylactic response (Palermo-Neto and Guimaraes, 2000)	Breathing pattern indicative of asthmatic attack (Noelpp and Noelpp-Eschenhagen, 1951a), rearing behavior (Palermo-Neto and Guimaraes, 2000), freely acting plus maze behavior (Palermo-Neto and Guimaraes, 2000)
			Physiological	Plasma histamine levels (Dark et al., 1987; Irie et al., 2001, 2002a, 2002b, 2004; Peeke et al., 1987a, b; Russell et al., 1984), lung tissue histamine levels (Irie et al., 2001), rat mast cell protease II (MacQueen et al., 1989), plasma cortisol levels (Peeke et al., 1987a), plethysmographic amplitude (Justesen et al., 1970), corticosterone levels (Palermo-Neto and Guimaraes, 2000)	Plasma histamine levels (Irie et al., 2001), bronchoalveolar lavage fluid (Irie et al., 2001), respiratory resistance (Irie et al., 2002a)
		Operant conditioning	Behavioral	Scratching behavior (Pearce et al., 1978)	Scratching behavior (Morgan and Nicholas, 1979)
		Social induction	Behavioral	Scratching behavior (Feneran et al., 2013; Nakayama, 2004; Yu et al., 2017), attention (looking behavior) (Whitehouse et al., 2016)	Scratching behavior (Whitehouse et al., 2016), attention (looking behavior) (Yu et al., 2017)
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 (Zachariae and Bjerring, 1990)	
			Physiological	Wheal area (Prausnitz-Küstner reaction to horse serum) (Black, 1963b), wheal area to histamine (Laidlaw et al., 1996), titration gradients (Laidlaw et al., 1996), histaminergic flare (Zachariae and Bjerring, 1990; Zachariae et al., 1989), Mantoux skin response (Zachariae et al., 1989)	Titration endpoint data (Laidlaw et al., 1996), wheal/erythema ratio (Locke et al., 1987, 1994), histamine wheal (Zachariae et al., 1989), erythema (Zachariae and Bjerring, 1993), skin thickness (Zachariae and Bjerring, 1993)
		Verbal suggestions	Self-reported	Expected wheal area (Darragh et al., 2013), self-rated itch in response to histamine (Darragh et al., 2015b), expected itch (Peerdeman et al., 2015; Skvortsova et al., 2018), expected pain (Peerdeman et al., 2015; Skvortsova et al., 2018), expected fatigue (Peerdeman et al., 2015), self-rated pain during CPT (Skvortsova et al., 2018), mechanically induced itch (van Laarhoven et al., 2011), electrically induced itch (van Laarhoven et al., 2011), chemically induced itch (histamine) (van Laarhoven et al., 2011), mechanically induced pain (van Laarhoven et al., 2011), electrically induced pain (van Laarhoven et al., 2011), chemically induced pain (histamine) (van Laarhoven et al., 2011)	Itch + anxiety levels not described (Howe et al., 2017) Self-rated itch (Peerdeman et al., 2015; Skvortsova et al., 2018), self-rated pain (Peerdeman et al., 2015), self-rated fatigue (Peerdeman et al., 2015), physical sensitivity (Peerdeman et al., 2015), chemically induced itch (histamine) (van Laarhoven et al., 2011)

Table 1 (*continued*)

Sample type	Type of induction	Mechanism(s)	Outcome category	Outcome classification — Confirmation of hypothesis*	Non-confirmation of hypothesis**
			Physiological	Heart rate (Darragh et al., 2013), histamine wheal area (Howe et al., 2017), histaminergic flare (Howe et al., 2017)	Histamine wheal area (Darragh et al., 2013, 2015b; Skvortsova et al., 2018), heart rate variability (Darragh et al., 2013), heart rate (Peerdeman et al., 2015), skin conductance (Peerdeman et al., 2015), skin temperature (Skvortsova et al., 2018)
		Verbal suggestions (OL)	Self-reported	Expected itch (Meeuwis et al., 2018)	Self-rated itch in response to histamine (Meeuwis et al., 2018), self-reported skin response (Meeuwis et al., 2018)
			Physiological	–	Wheal area (Meeuwis et al., 2018), flare area (Meeuwis et al., 2018)
		Conditioning (+ VS)	Self-reported	Electrically induced itch (Bartels et al., 2014)	–
	Nocebo	Verbal suggestions	Self-reported	Self-rated itch (Stumpf et al., 2016), self-rated unpleasantness (Stumpf et al, 2016)	–
			Physiological	Wheal intensity (NaCl) (Stumpf et al., 2016), histaminergic flare intensity (Stumpf et al., 2016)	–
		Conditioning (+ VS)	Self-reported	Self-rated itch (Bartels et al., 2017; van de Sand et al., 2018)	–
			Physiological	fMRI: activity in contralateral rolandic operculum (van de Sand et al., 2018), functional coupling between periaqueductal gray (van de Sand et al., 2018)	–
		Social induction	Self-reported	Self-rated itch (Holle et al., 2012; Lloyd et al., 2012; Mitchell, 1995)	–
			Behavioral	Scratching (Holle et al., 2012; Lloyd et al., 2012; Mitchell, 1995) fMRI: activation of major areas of itch matrix (thalamus, primary somatosensory cortex, premotor cortex, insula) (Holle et al., 2012)	–
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 (Hájek et al., 1990), atopic eczema symptoms (Hájek et al., 1990), retrospectively assessed symptoms of allergy (Langewitz et al., 2005), nasal flow symptoms during challenge (NPT) (Langewitz et al., 2005), self-rated itch (Shertzer and Lookingbill, 1987)	Daily self-report symptoms of allergy (Langewitz et al., 2005), nasal flow symptoms after challenge (NPT) (Langewitz et al., 2005)
			Physiological	Skin temperature (Black, 1963a), skinfold thickness (Black, 1963a), allergen-induced wheal size (Fry et al., 1964), allergen induced flare size (Fry et al., 1964), histaminergic flare size (Laidlaw et al., 1994), number of warts**** (Sinclair-Gieben and Chalmers, 1959; Surman et al., 1973; Ullman and Dudek, 1960)	Allergen-induced wheal size (Fry et al., 1964), allergen induced flare size (Fry et al., 1964), histamine wheal size (Laidlaw et al., 1994; Levine et al., 1966), histaminergic flare (Levine et al., 1966), phosphate dilutions (Levine et al., 1966), number of urticaria wheals (Shertzer and Lookingbill, 1987), clinical psoriasis severity (Tausk and Whitmore, 1999), delayed blanch of skin (West et al., 1961), histaminergic flare (West et al., 1961), white line response (West et al., 1961)
		Verbal suggestions (OL, + inert pill)	Self-reported	Allergic symptoms composite score (Schaefer et al., 2016, 2018)	Allergic symptoms: separate scores (Schaefer et al., 2016)
		Pharmacological conditioning / conditioned dose reduction	Self-reported	Psoriasis severity scale (Ader et al., 2010)	Allergic symptoms (Goebel et al., 2008), Allergic symptoms in response to NPT (Vits et al., 2013)

(*continued on next page*)

Table 1 (*continued*)

Sample type	Type of induction	Mechanism(s)	Outcome category	Outcome classification — Confirmation of hypothesis*	Non-confirmation of hypothesis**
			Physiological	Psoriasis relapse (Ader et al., 2010), basophil activation (Goebel et al., 2008)	Wheal size in response to allergens (Goebel et al., 2008; Vits et al., 2013), blood count & flow cytometry (Goebel et al., 2008)
		Conditioning (+ VS)	Self-reported	Pain in response to electrical stimulation (Klinger et al., 2007)	–
		Social induction	Physiological	Wheal size in response to histamine (Kamenica et al., 2013)	–
	Nocebo	Verbal suggestions + hypnosis	Physiological	Skin temperature (Hájek et al., 1992)	–
		Verbal suggestions	Self-reported	Self-rated itch (Napadow et al., 2015)	–
			Physiological	Conductance – thoracic gas volume ratio (Luparello et al., 1968; McFadden et al., 1969), airway resistance (Luparello et al., 1968; McFadden et al., 1969); fMRI: increase in dorsolateral prefrontal cortex, caudate, and intraparietal sulcus (Napadow et al., 2015)	Wright-McKerrow Peak Flow Meter outcomes (Weiss et al., 1970), maximum expiratory flow rate (Weiss et al., 1970), respiratory pattern (Weiss et al., 1970)
		Conditioning [A]	Self-reported		Subjective allergic symptoms (Barrett et al., 2000; Gauci et al., 1994)
			Physiological	Peak nasal inspiratory flow (Barrett et al., 2000), blood serum histamine levels (Barrett et al., 2000), nasal tryptase levels (Gauci et al., 1994)	Wheal size in response to sham allergen (Booth et al., 1995)
		Social induction	Self-reported	Self-rated itch (Niemeier and Gieler, 2000; Papoiu et al., 2011; Schut et al., 2014, 2017)	Self-rated itch (HC only) (Papoiu et al., 2011)
			Behavioral	Scratching behavior (Niemeier and Gieler, 2000; Papoiu et al., 2011; Schut et al., 2014, 2017), allergic symptoms (von Leupoldt and Dahme, 2012)	–
			Physiological	Breathing frequency (von Leupoldt and Dahme, 2012); fMRI: higher activity in supplementary motor area, the left ventral striatum and higher right orbitofrontal cortex activation (Schut et al., 2017)	Airflow (von Leupoldt and Dahme, 2012), tidal volume (von Leupoldt and Dahme, 2012), inspiratory time (von Leupoldt and Dahme, 2012), respiratory resistance (von Leupoldt and Dahme, 2012)

Note. * 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 change 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.

volunteers and patient studies) in Supplementary Tables S2–S4.

3.2. Risk of bias assessment

An overview of the risk of bias assessment outcomes is provided separately for animal and human studies, in Supplementary Figs. S2–S5. The quality of the 86 included studies varied. None of the included animal studies scored low risk on 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.

3.3. 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 %).

3.3.1. Placebo effects
3.3.1.1. 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 (Roudebush and Bryant, 1991). One study found extinction of conditioned responses following the first of three re-exposures (Bovbjerg et al., 1987). Moreover, one study indicated that conditioned effects are dependent on the induction of stress (Kelley et al., 1985), suggesting that conditioned responses may be context-specific.

3.3.2. Nocebo effects
3.3.2.1. 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 (Noelpp and Noelpp-Eschenhagen, 1951a), while another found conditional effects: exposure to the CS led towards asthmatic attacks

– but only when animals were stressed (Noelpp and Noelpp-Eschenhagen, 1951b). It was demonstrated that freely-acting behavior (e.g., rearing, locomotion) did not change following conditioning (Palermo-Neto and Guimaraes, 2000). 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 (Irie et al., 2001, 2002a). Others showed mixed evidence for conditioned histamine release in rodents: it was shown that effects depended on handling-induced stress (Dark et al., 1987; Peeke et al., 1987a), fasting stress (Irie et al., 2002a), anesthetization (Irie et al., 2001), or receiving medication such as diazepam (Irie et al., 2004) or dexamethasone (Peeke et al., 1987b). For example, conditioned histamine release occurred exclusively in stressed animals.

3.3.2.2. (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 (Morgan and Nicholas, 1979; Pearce et al., 1978). One study found scratching to be less readily conditioned compared to rearing or washing (Morgan and Nicholas, 1979), 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 (Pearce et al., 1978).

3.3.2.3. 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 study 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 (Feneran et al., 2013; Yu et al., 2017), while two other studies found that scratching did not increase following observation of another animal scratching (Nakayama, 2004; Whitehouse et al., 2016).

3.4. 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) and three studies (14 %) investigated females exclusively. Sample sizes ranged between 10–159 healthy volunteers. Most studies were conducted in the past 10 years (2010 − 2019: k = 13, 64 %).

3.4.1. 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 '3.4.1.2. Conditioning').

3.4.1.1. 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) (Zachariae and Bjerring, 1990) 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) (Black, 1963b; Laidlaw et al., 1996; Zachariae and Bjerring, 1990). One study found that effects on wheal area were a function of the depth of the trance induced by

hypnosis (Black, 1963b). 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 (Locke et al., 1987, 1994; Zachariae and Bjerring, 1993; Zachariae et al., 1989). Only one study reported significant differences in skin thickness following suggestions at certain dilution strengths of the test substance (Zachariae et al., 1989). 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 (Darragh et al., 2013, 2015b; Peerdeman et al., 2015; Skvortsova et al., 2018). Three studies assessed histamine-induced itch (Darragh et al., 2015b; Peerdeman et al., 2015; Skvortsova et al., 2018), but only one of these found lower itch following suggestions (Darragh et al., 2015b). Positive suggestions reduced pain during a cold-pressor task in one study (Skvortsova et al., 2018), but not in another (Peerdeman et al., 2015). Wheal area was not affected by suggestions in any study. Two studies compared positive suggestions with negative suggestions (Howe et al., 2017; van Laarhoven et al., 2011): 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 (van Laarhoven et al., 2011). 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 (Howe et al., 2017).

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 (Meeuwis et al., 2018). Suggestions decreased itch expectations, but not itch. No effects on physical skin response (histaminergic flare (area), skin temperature, wheal area) were found.

3.4.1.2. 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 (Bartels et al., 2014).

3.4.2. 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 '3.4.2.2. conditioning'[1]), or by social cues (k = 3; contagious itch).

3.4.2.1. 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 (Stumpf et al., 2016). 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 (Stumpf et al., 2016).

3.4.2.2. 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 (Bartels et al., 2017). Two studies found that conditioning and verbal suggestions could both increase itch (Bartels et al., 2014; van de Sand et al., 2018). In addition, one of these reported that a combination was most effective to induce nocebo effects (Bartels et al., 2014). 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 (van de Sand et al., 2018).

3.4.2.3. 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 (Holle et al., 2012), slideshows of itch-related pictures (Lloyd et al., 2012), or itch suggestions during music, which were presented either sub- or supraliminally (Mitchell, 1995). Itch and scratching behavior were increased in 2 of 3 studies (Holle et al., 2012; Lloyd et al., 2012). In the remaining study, findings were mixed: itch and scratching were increased only when suggestions were presented supraliminally during music, but not when presented subliminally (Mitchell, 1995). 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 (Holle et al., 2012).

3.5. Patient studies

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 %).

3.5.1. 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).

3.5.1.1. 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) (Hájek et al., 1990; Langewitz et al., 2005; Shertzer and Lookingbill, 1987). 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 (Black, 1963a; Fry et al., 1964; Surman et al., 1973). 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

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[1] This includes the study of Bartels et al. (2014) that is also described under subsection '3.4.1. placebo effects', as both placebo and nocebo effects were investigated within this study.

statistical tests were reported (Sinclair-Gieben and Chalmers, 1959). Some studies noted that symptoms improved only when deep hypnosis was achieved (Tausk and Whitmore, 1999; Ullman and Dudek, 1960).

Finally, two studies investigated whether open-label placebo effects could be induced for allergic rhinitis (Schaefer et al., 2016, 2018). A briefing about the placebo effect was given together with inert pills (in addition to treatment as usual) in one study (Schaefer et al., 2016). In the other, both separate and combined effects of the briefing and the inert pills were examined (Schaefer et al., 2018). 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 (Schaefer et al., 2018).

3.5.1.2. 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 (Goebel et al., 2008; Vits et al., 2013). Basophil activation after exposure to allergens was reduced, however, which is indicative of conditioned immunosuppression (Goebel et al., 2008). 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 (Ader et al., 2010). 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 (Klinger et al., 2007). Verbal suggestions, but not conditioning, reduced pain in both atopic dermatitis and healthy controls. Moreover, a combination of suggestions and conditioning was most effective.

3.5.1.3. 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 (Kamenica et al., 2013). 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 min 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 min following antihistamine use.

3.5.2. 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).

3.5.2.1. 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 (Hájek et al., 1992). Another study in atopic dermatitis investigated nocebo effects induction by suggestions exclusively, and found that this increased self-reported itch (Napadow et al., 2015). 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 (Napadow et al., 2015). Finally, three studies investigated effects of negative suggestions on physiological parameters representing airway reactivity (Luparello et al., 1968; McFadden et al., 1969; Weiss et al., 1970). One study failed to find effects of negative suggestions on physiological parameters (i.e., respiratory pattern, maximum expiratory flow) in bronchial asthma (Weiss et al., 1970). 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 (Luparello et al., 1968; McFadden et al., 1969). Moreover, positive suggestions (i.e., that a bronchodilator was given) reversed these effects (McFadden et al., 1969).

3.5.2.2. 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 (Barrett et al., 2000; Gauci et al., 1994). Physiological parameters (i.e., peak nasal inspiratory flow, histamine level, nasal tryptase level) increased following conditioning in 2 studies (Barrett et al., 2000; Gauci et al., 1994), while another failed to find effects (i.e., for wheal response to sham allergens) (Booth et al., 1995). Generally, conditioned effects were stronger when the number of acquisition trials increased, and effects were prone to extinction (Barrett et al., 2000). Finally, for patients with atopic dermatitis and lichen simplex, conditioning led to a higher number of scratch responses compared to healthy controls (Jordan and Whitlock, 1972; Roberston et al., 1975).

3.5.2.3. 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 (Niemeier and Gieler, 2000; Papoiu et al., 2011; Schut et al., 2014, 2017). 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 (Schut et al., 2017). While breathing frequency increased in response to allergen pictures in allergic asthma, no changes were detected for other (physiological) respiratory parameters (von Leupoldt and Dahme, 2012).

4. 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 with 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 (Bovbjerg et al., 1987; Dark et al., 1987; Irie et al., 2001, 2002a, 2004; Kelley et al., 1985; Peeke et al., 1987a, b). 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 (Blythe et al., 2019; van Laarhoven et al., 2019). 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 (Benedetti et al., 2018). 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 (Holle et al., 2012; Napadow et al., 2015; Schut et al., 2017; van de Sand et al., 2018). 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 (Schut et al.,

2015). 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 (Bartels et al., 2016; Blythe et al., 2019; Wolters et al., 2019), 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 (Rief et al., 2011), could be considered most directly applicable in clinical practice (Enck et al., 2013), 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 (Ader et al., 2010; Sandler et al., 2010). 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 (Meeuwis et al., 2019a, b; Meeuwis et al., 2018; Schaefer et al., 2016, 2018), 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 (Carvalho et al., 2016; Charlesworth et al., 2017; Kaptchuk et al., 2010; Kelley et al., 2012; Sandler and Bodfish, 2008). 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 (Blease et al., 2016). 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 (Bartels et al., 2017). Studies in other research areas (e.g., in the field of pain) also show promising results for such methods (Manaï et al., 2019). 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 (Manaï et al., 2019). 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 (Vits et al., 2013). Likewise, there is evidence that individual characteristics, such as personality characteristics and polymorphisms in genetic markers, may impact placebo and nocebo effects (Colagiuri et al., 2015; Colloca and Miller, 2011; Darragh et al., 2015a; Frisaldi et al., 2018; Peerdeman et al., 2016), although evidence for these specific predictors of placebo and nocebo effects within the field of dermatology is limited and mixed (Bartels et al., 2016). 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 (Tausk and Whitmore, 1999; Ullman and Dudek, 1960). 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 (Stumpf et al., 2016). 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 et al. (2016).

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.

Funding

Author contributions

SM, HvM, AvL and AE designed the review. SM, AvL, HvM, AL, DV and GPL constructed the search terms. SM carried out the literature search. SM and CvL assessed retrieved papers on eligibility and screened reference lists for relevant papers. SM extracted data from the included papers. SM conducted the risk of bias analyses (with KB – see acknowledgements). SM and HvM drafted the manuscript and were provided feedback by AvL, DV, AL, GPL, CvL and AE. All authors contributed to the final manuscript and all read and approved the final manuscript.

Declaration of Competing Interest

None.

Acknowledgements

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.03.025.

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