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

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Chapter 7

Summary and General Discussion

SUMMARY

The aim of this dissertation was to investigate the induction of placebo and nocebo effects for histaminergic itch based on multiple approaches of associative and instructional learning. Pharmacological conditioning and positive and negative verbal suggestions were used to elicit effects in both open-label (i.e., with participants knowing about the placebo or nocebo effect induction) and closed-label (i.e., concealed, or with participants not knowing about the placebo or nocebo effect induction) contexts. Moreover, effects of these approaches on other (psycho)physiological responses to histamine were addressed.

With regard to the dissertation aim, **Chapter 2** examined the existing literature on experimentally elicited placebo and nocebo effects in itch, and itch-related medical conditions and symptoms of the dermis and mucous membranes, as well as in related animal and human models. The systematic literature review covers the methods used to elicit these effects, as well as the general study findings. Broadly, placebo and nocebo effects have been elicited by three techniques, or combinations thereof: verbal suggestions (with or without hypnosis), (classical or operant) conditioning, and social learning (e.g., induction of contagious itch). Overall, these methods were successful in eliciting placebo and nocebo effects for itch and itch-related symptoms within dermatology. However, the review also shows that studies are largely heterogeneous, and that the elicited placebo and nocebo effects are oftentimes conditional: for example, conditioned placebo and nocebo effects are subject to changes in the context in which effects are learned, and verbal suggestions seem to elicit effects only on the short term. A large variety of procedures (i.e., no standard 'conditioning protocol', or standard suggestions) for placebo and nocebo effects induction was found, regardless of which type of technique was used, and effects were investigated in very diverse patient populations, as well as in different animal and human models.

In **Chapter 3,** the results of a randomized controlled study on the classical (pharmacological) conditioning of the antipruritic effects of H1-antihistamines were reported. Pharmacological conditioning is one of the mechanisms by which placebo effects can be induced. Two previous studies have investigated conditioning of antihistamines in allergic patients, but were unable to distinguish between conditioned and other expectancy effects on self-reported allergic symptoms. The study described in this chapter aimed to fill this knowledge gap by investigating conditioned effects for histamine-evoked itch and other histamine-related parameters in healthy volunteers. Although conditioning resulted in

marginal lower itch compared with control, no differences between separate groups were found, nor did conditioning influence other parameters in the study under either open-label or closed-label conditions. Overall, the study provides limited evidence for the antipruritic effects of conditioning with H1-antihistamines.

In **Chapters 4, 5, and 6**, three studies were described in which the effects of verbal suggestions on itch and other (psycho)physiological responses to histamine were examined. In **Chapter 4**, the effects of open-label positive verbal suggestions about low itch were compared with neutral instructions. While no differences between groups were found, expected and experienced itch were significantly related following verbal suggestions exclusively. Moreover, a trend was observed for self-assessed skin condition, with open-label positive suggestions resulting in marginal lower self-assessed skin condition severity compared with neutral instructions. As a whole, these results illustrate a potential role for open-label placebo effects in itch (as evidenced by the association between expected and experienced itch following positive suggestions).

In **Chapter 5**, the effects of open-label and closed-label positive and negative verbal suggestions about the itch-reducing (or –increasing, depending on group allocation) properties of an (inert) tonic on itch were compared. No effects on itch during histamine iontophoresis were found, but itch during a short follow-up period was lower in the positive compared with the negative verbal suggestions groups, both in open-label and closed-label contexts. Further examination of the data indicated that in the positive suggestion groups, itch reduced significantly, whereas in the negative suggestion groups, no changes were found. These results indicate that placebo and nocebo effects may be elicited for itch by verbal suggestions in both open-label and closed-label contexts, though future research on these effects is warranted.

In **Chapter 6,** effects of open-label and closed-label positive and negative verbal suggestions were again compared for itch, with the suggestions being that itch would be influenced as a side effect of a (sham) transdermal caffeine patch. In short, verbal suggestions resulted in significant changes in the amount of itch that was experienced for both open-label and closed-label contexts, thus showing that these effects can be induced when people know about them. As in **Chapter 5**, further examination of baseline-to-post-VS changes shows that itch significantly reduced in the positive VS groups, but did not change following negative suggestions. Taken together, these findings demonstrate

effective placebo and nocebo effect induction for itch under both open-label and closed-label contexts.

Taken together, the performed studies investigated experimental elicitation of placebo and nocebo effects using various methodological approaches. The studies examined the existing literature on this topic (**Chapter 2**) and whether effects could be elicited by pharmacological conditioning (**Chapter 3**) or by verbal suggestions (**Chapter 4-6**). Finally, they examined the potential of eliciting effects with participants' awareness. In the following section, we discuss the results of this dissertation, mention limitations that may be addressed in future research, and discuss several clinical implications and the scientific relevance of the work.

GENERAL DISCUSSION

The systematic review in **Chapter 2** indicated that placebo and nocebo effects have been investigated in itch and itch-related medical conditions and symptoms of the dermis and mucous membranes using a wide range of induction methods in patient samples, and in relevant animal and human (i.e., healthy participants) models. Three main categories of placebo and nocebo effects induction could be identified: associative learning (i.e., conditioning), instructional learning (i.e., verbal suggestions), and social learning (i.e., social cues). Verbal suggestions were used to investigate placebo and nocebo effects in human trials with study groups of patients, healthy participants, or both. From the systematic literature review, we concluded that there is evidence for the efficacy of verbal suggestions for eliciting both placebo effects and nocebo effects, however, the methods often differ between studies, and effects of suggestions on physiological outcomes are by and large lacking. Secondly, animal and human studies (in healthy participants and patients) showed both placebo (e.g., immunosuppression) and nocebo (e.g., exacerbation of allergic responses, or scratching behavior) effects on physiological and behavioral parameters through classical conditioning. For self-reported outcomes such as allergic symptoms and self-rated itch in human trials, conditioning of negative (nocebo) effects could be demonstrated. However, conditioning of positive (placebo) responses appeared more complicated. One explanation for such a phenomenon may be that learning of negative associations could be more potent and therefore needs less acquisition trials than the learning of positive associations. From an evolutionary perspective, this explanation

would be sensible, considering that rapid learning of and responding to negative stimuli (i.e., threats) might be directly linked to an individual's and species' survival [1-4]. Finally, itch may also be prone to be influenced by social factors, as evidenced by successful induction of contagious itch and the impact that advertisements for different brands of antihistamines were demonstrated to have on reporting of allergic symptoms during antihistamine treatment.

Overall, the existing literature demonstrates ample evidence for placebo and nocebo effects in itch and itch-related conditions and symptoms. However, the body of evidence currently available is also characterized by a large heterogeneity in both methodology and chosen outcome parameters – which makes it challenging to extend findings across dermatological conditions. The current dissertation builds on these previous findings and investigates placebo and nocebo effects for histamine-induced itch in healthy volunteers using conditioning and verbal suggestions. Previous studies used pharmacological conditioning to elicit placebo effects to enhance clinical outcomes in patients diagnosed with psoriasis [5] or allergic rhinitis [6,7]. However, these studies have investigated the efficacy of conditioning for a multitude of symptoms, including itch. This may complicate an exact interpretation of study findings, since symptoms could be susceptible to changes caused by multiple factors that are unrelated to the study aim (e.g., regression to the mean, spontaneous recovery). Moreover, symptoms may be elicited through various pathways (e.g., both histaminergic and non-histaminergic itch pathways). It may then be challenging to ascribe symptom change to a single isolated mechanism such as conditioning with, for example, antihistamines. The effects of pharmacological conditioning of antihistamines have not yet been tested in experimental models that exclusively induce histaminergic itch in healthy volunteers.

Previous work with healthy volunteers also shows that itch may be reduced by providing positive verbal suggestions [8], and that negative verbal suggestions could increase itch [9-11], but itch induction methods differ between studies and it may be challenging to translate study findings to clinical practice. This dissertation extends the previous findings by investigating the efficacy of conditioning and verbal suggestions for itch under open-label conditions (i.e. non-concealed). Potentially, eliciting placebo effects while patients are aware of this may lead to new therapeutic possibilities aimed at maximizing treatment efficacy and minimizing adverse events.

Experimental induction of placebo and nocebo effects for itch

Associative learning: antipruritic conditioning of H1-antihistamines

Previous work shows that allergic responses can be exacerbated by conditioning in patients [12-14], and that immunosuppressive properties of medications may be sensitive to conditioning effects as well. Studies find that the effects of general immunosuppressive agents – for instance, of cyclosporine-A (CsA) – can be mimicked using conditioning mechanisms in humans: when only a conditioned stimulus (CS) is presented, similar effects are found compared with previous exposures, where the CS was presented together with CsA as unconditioned stimulus (UCS) [3,15,16]. For example, conditioning with CsA has been found to result in reduced levels of interleukin-2 and, in some studies, also reductions of IFN-γ [3,17,18]. Considering that exacerbation of allergic responses can also be conditioned, and considering the potential of conditioned (general) immunosuppression, it stood to reason that a reduction of allergic symptoms may also be conditioned. Two studies investigated this hypothesis by classically conditioning the effects of antihistamines in allergic patients, and reported mixed results: although a unique physiological conditioned response (i.e. reduced basophil activation) was found in one study [6], no distinctive effects for self-reported allergic symptoms and physical skin responses were identified [6,7]. It should be noted that one study showed these subjective outcomes reduced over time in both the conditioned and sham-conditioned groups, compared with a natural history group – thus implying that other factors, for example conscious expectancy, could have impacted outcomes [7]. For example, natural fluctuations in allergic symptoms may have been interpreted as medication effects and may thus have potentially interfered with the study protocol.

The study reported in **Chapter 3** builds on the findings of these two studies and investigated whether conditioning with H1-antihistamines could influence itch that was experimentally elicited by histamine and other (psycho)physiological parameters in healthy volunteers. In addition, the study investigated the efficacy of conditioning when participants were aware of the conditioning procedures (open-label). A conditioning protocol was applied with three acquisition moments and three evocation moments. Effects of conditioning on psychological and physiological parameters were examined, as were effects of conditioning during a short term histamine challenge, in which itch was experimentally elicited on the skin of the forearm during a short period of time. Limited evidence for conditioning of H1-antihistamines in reducing histamine-induced itch was

found, while no effects of conditioning were found for any of the other parameters in the study. Potentially, conditioned responses may have been small, as the sample consisted of healthy participants who did not experience allergic symptoms prior to enrolment in the study – this may have led to a situation in which the unconditioned response (effects of levocetirizine) may not have been easily noticeable. Consequently, learned responses would also be small, or associations between the CS and UCS may not have readily formed (as previously discussed in **Chapter 3**). This would be in line with theoretical models that place expectancy at the center of placebo effects as they state that, in order to learn, awareness (of both causes and effects) is needed [19]. There is some evidence that challenges such models, however, as conditioning has been found to result in hyperalgesia and analgesia when the CS was presented on a subliminal (i.e. subconscious) level [19,20]. This would imply that it may hypothetically be possible to unconsciously condition endogenous responses through pharmacological means as well. This notion is supported by the marginal reduction in itch that was found in the conditioned groups of the study in **Chapter 3**. It should be noted though that this reduction in itch was not significant – for clinically relevant effects, awareness may be needed regardless. Alternatively, it may be possible that immunosuppressive conditioning needs more acquisition trials for stronger effects compared to the conditioning of negative events (e.g., allergic responses, other enhanced immune reactions), as immunosuppression may be less sensitive to conditioning [21]. From an evolutionary perspective, rapid learning of negative associations helps in the survival of organisms whereas positive associations may be less relevant and thus less salient for behavioral conditioning [1-4]. Moreover, measures of itch were taken on the third evocation day. It may be possible that (partial) extinction of the conditioned response had already taken place at that moment. For example, this has been shown in a study on conditioned endocrine responses, that used a similar design [22]. Future research could investigate whether antipruritic conditioned effects of antihistamines may be stronger at earlier evocation moments, or investigate what factors could help strengthen placebo effects elicited by antipruritic conditioning of antihistamines (e.g., a longer acquisition phase, itch induction during acquisition to boost learning).

Instructional learning: verbal suggestions about itch and itch-related treatments

Instructional learning, for example by verbal suggestions, may also be a potential mechanism by which placebo (and nocebo) effects could be elicited. As described in

Chapter 2, verbal suggestions can influence levels of itch, but some uncertainty exists about under which circumstances verbal suggestions may induce placebo or nocebo effects. In most experimental studies, the verbal suggestions are modelled after a situation in the clinic. Broadly, three different categories of information modelling can be discerned (see also **Table 1**): I. information about symptoms elicited by a test (**Chapter 4** – as these suggestions are open-label exclusively, this category will be discussed in the following section), II. information about the intentional effects of a treatment method (**Chapter 5**), or III. information about the unintentional effects of a treatment method (e.g., side effects; **Chapter 6**).

In **Chapters 5 and 6**, effects of concealed positive and negative verbal suggestions on itch elicited by a short-term histamine challenge were examined using different categories of information modelling. In **Chapter 5**, participants were told that the effects of a tonic on sensitivity of the skin to itch would be examined. Depending on group allocation, participants were then told that itch would either increase or decrease following the application of a (sham) tonic, making the proposed effects on itch a direct consequence of the intended treatment (Table 1: 'model 2'). In **Chapter 6**, participants were told that the study investigated effects of a transdermal caffeine patch on cognitive functioning, and that *as a side effect*, this would impact sensitivity to somatic symptoms such as itch. As such, proposed positive or negative effects on itch were introduced as an inadvertent consequence of a treatment rather than the intended effects (Table 1: 'model 3'). Overall, both types of suggestions were found to impact itch either during histamine application, or in a short follow-up period after the test. The two ways in which information was provided mirror those often used in consults with patients, where health care providers explain effects of a treatment as well as potential side effects that may be expected.

For itch specifically, there are relatively few studies that have investigated effects of positive verbal suggestions about a treatment on itch. A single study showed that suggestions about a cream were able to elicit placebo effects for itch [8]. The study described in **Chapter 5** is in line with this work and extends these previous findings by showing that verbal information about a different type of topical treatment (i.e., a 'tonic') can also influence itch in a short follow-up period to histamine iontophoresis. It should be noted though that itch during iontophoresis was not significantly influenced by positive and negative verbal suggestions. Potentially, the suggestions may not have been convincing enough to significantly influence itch during the test (e.g., participants were told that the tonic would influence itch, but were not involved about why it would work, or what active

component in the tonic would cause this). Nonetheless, the results of this study as a whole highlight a potential role of verbal suggestions in eliciting placebo and nocebo effects for itch.

In **Chapter 6**, placebo and nocebo effects were elicited by providing information about itch as a side effect of a transdermal caffeine patch. Relatively few studies investigate whether nocebo effects can be elicited by providing side effect information in experimental settings. However, it has been demonstrated that the manner in which side effect information is framed can impact the frequency and severity of several drug-related side effects (see, for example, [34-38]). Although information framing has not been formally investigated for itch yet, the study findings described in **Chapter 6** appear consistent with this line of research. For instance, it is shown that directional (i.e., positive or negative) information about itch as a side effect can directly impact the intensity of itch experienced by participants. Noticeably, significantly reduced itch was found following positive suggestions in **Chapter 6,** but itch did not increase following negative suggestions. This may be explained by the specific study procedures however (i.e., repeated itch provocations may result in lower itch by itself). Overall, the findings in **Chapter 6** show that information about itch as a side effect may impact itch experience.

Taken together, the studies described in **Chapter 5 and 6** demonstrate that providing positive and negative verbal information can influence the experience of itch in experimental settings. This emphasizes that the type and manner in which information is provided could potentially be used to maximize treatment efficacy, by enhancing positive expectations about treatments and eliciting placebo effects. It furthermore shows that it is important to carefully consider the manner in which negative information should be provided in the clinic. Finally, the findings demonstrate that healthcare providers may be able to actively contribute to treatment efficacy by the manner in which they communicate about treatment. However, future research is needed in order to more precisely estimate placebo and nocebo effect sizes, and to investigate whether variations in instructions may impact these effect sizes.

Table 1. Categories of information modelling

Model	Category of information modelling	Situation in the clinic (example)	Experimental placebo or nocebo model (example)	Previous work (example)	Dissertation chapter
1	Information about symptoms that are elicited by a test	Explaining a medical procedure, for example, skin prick tests for allergy, or explaining discomfort caused by blood sampling	Verbal suggestions about a sham device or itch induction method (e.g., "this [device/method] will elicit itch for most people")	*Closed-label* [9-11, 23-27]	Chapter 4 (*open-label exclusively*)
2	Information about the intentional effects of a treatment method	Consults with patients in which information is given about (new) treatments (i.e., what effects to expect from the treatment)	Verbal suggestions about an inert substance, such as a cream or pill, and its effects on experimental elicitation of itch (e.g., "this cream will reduce itch")	*Open-label* [28, 29] *Closed-label* [8, 30-33]	Chapter 5 (*both open- and closed-label*)
3	Information about the unintentional effects of a treatment method [a]	Consults with patients in which information is given about *side effects* that can be expected with a certain treatment, leaflet information	Verbal suggestions about side effects of an inert treatment method (e.g., "this medication can elicit side effects such as headaches")		Chapter 6 (*both open- and closed-label*)

Note: [a] To our knowledge, no previous studies have investigated experimental elicitation of placebo and nocebo effects by verbal suggestions about side effects. However, previous work on information framing and nocebo effects (e.g., [34-38]) suggests that the manner in which information is provided can influence the severity of experienced side effects.

Open-label placebo and nocebo effects

There has been a lot of debate on how to ethically use the knowledge of placebo and nocebo effects in clinical practice [39-42]. Central to this debate is the concept of deception: the notion that the deceptive nature of experimental placebo and nocebo effects induction would complicate direct application of this knowledge in clinical practice, as patients need to be fully informed about treatments for ethical medical treatment [39-42]. Over the years, various solutions to this conundrum have been proposed, including having patients provide consent for informed deception during treatment (e.g., so conditioning mechanisms can be used to enhance placebo effects), or providing patients with minimal information about side effects during consults, and offering them the option to look up information elsewhere (to minimize nocebo effects) [43]. Another promising angle of approach is through eliciting placebo effects without deception [39,44].

Studies have found that open-label placebo effects can be elicited for symptoms of various conditions, including irritable bowel syndrome, allergic rhinitis, chronic low back pain, ADHD, and depression [28,29,45-55]. Central to most of these studies is the combination of giving inert pills and providing a rationale with four key arguments: 1) that placebo effects may be powerful, 2) that these effects may be learned through Pavlovian conditioning, 3) that positive attitudes are not necessary, but may be helpful to induce effects, and 4) that pills need to be taken faithfully (i.e., adherence) [45]. Overall, the studies show promising effects, but with regard to the type of open-label placebo effect induction, little is still known about the underlying mechanisms. A single study has teased apart the effects of the open-label placebo rationale and the inert pills, and found that the inert pills seemed to elicit effects, whereas the added rationale did not significantly contribute to placebo effects [28]. This would imply that effects may be mostly due to previous associations between the medical ritual of ingesting a pill and reduction of symptoms. Another study has shown that only groups that receive a rationale appear to benefit on subjective symptoms, at least when a cream is used as inert substance [52]. These discrepancies may be influenced by previously learned associations between application routes and efficacy for certain types of symptoms [57]. Relatively little is known about how variations in instructions and instruments (i.e., pills, creams, or other medication types) may impact open-label placebo effects, and effects have rarely been investigated for itch or itch-related conditions [28,29]. In the current dissertation, open-label placebo and nocebo effects were induced using various methods, which will be discussed below.

Associative learning: antipruritic conditioning under open-label conditions

The study described in **Chapter 3** aimed to investigate whether pharmacological conditioning of antihistamines could also be effective when participants knew about the conditioning procedure. While in general, participants in the open-label arm of this trial expected less itch during the histamine challenge compared with the other groups (who were not told about the conditioning procedure, and who were blinded to whether they received active medication), conditioning was able to only marginally influence itch levels. This complicates interpretations of the impact that the open-label rationale may have had on the efficacy of the conditioning procedure. Previous studies show that open-label pills may be used as a dose-extender. For example, Sandler and colleagues [56] showed that subclinical doses (50% decrease) of extended-release mixed amphetamine salts (MAS-XR) could reduce ADHD symptoms in children to a level comparable with a full dose, when MAS-XR was given together with open-label placebo pills as 'dose extenders'. For the open-label placebo pills, an explanation was given to participants of how they may impact treatment by eliciting placebo effects. While no classical conditioning procedure was used in this study, the information it yields may be used for future studies: making use of subclinical doses could potentially strengthen conditioned responses for itch as well. Finally, Schafer and colleagues [58] investigated whether revealing the conditioning procedure to participants would impact conditioned analgesia. They demonstrated that analgesia persisted, even when it was revealed that participants received a placebo, thus indicating that learned placebo effects can be robust. It should be noted though that these instructions were aimed at revealing deception, whereas the instructions used in **Chapter 3** of this dissertation were aimed at convincing participants of the efficacy of conditioning, with the purpose of strengthening expectancy effects and investigating whether placebo effects may be elicited by conditioning under open-label conditions. Revealing previously used deception may impede conditioning (i.e., conditioned effects were halved following the reveal in Schafer and colleagues' experiment [58]), may have the potential to elicit negative thoughts or emotions, and may perhaps erode trust in health care practice in the long term. When conditioning is transparently and adequately explained prior to starting a treatment in which these mechanisms are utilized, such negative consequences could hypothetically be minimized, although this needs to be confirmed by future research.

To our knowledge, the study described in **Chapter 3** was the first to combine classical conditioning with open-label instructions. Variations in the frequency and what type of open-label instructions about conditioning should be provided naturally need to be further investigated, in order to fully gauge the impact of such instructions on the efficacy of conditioning of antipruritic effects. For example, the open-label instructions in **Chapter 3** were repeated with every administration of the CS and UCS or placebo pill. Future research may examine whether this repetition of instructions is necessary. In addition, the current open-label rationale did not specifically touch upon the biological underpinnings of conditioned placebo effects. The level of detail needed to maximize both comprehensibility of the conditioning mechanisms and positive outcome expectations may be examined in future research as well.

Instructional learning: verbal suggestions about itch under open-label conditions

As described above, few studies on open-label placebo effects have made the distinction between effects of the open-label placebo rationale and the inert pills, and the ones that did show that the effects may depend on the type of instrument (e.g., inert pills or creams) used. For example, in one study placebo effects elicited for allergic symptoms were found to be induced by an inert pill, while an added open-label rationale (i.e., explanation of placebo effects) did not elicit effects [28]. Another study reported contradictory findings, however, with an open-label rationale that did elicit placebo effects for pain and an inert cream that did not [52]. Hypothetically, one would imply that associative learning could underlie effects (i.e., placebo effects elicited by performing ritualistic medicinal practices that are strongly associated with symptom relief, for example, taking pills for pain reduction), whereas the other would imply that the explanation of placebo effects underlies the effects (i.e., cognitively modulating expectancies for treatment by explaining the working mechanisms involved and the to-be-expected effects). There are too few studies conducted in this field – with too little variation in instructions and instruments – to draw any firm conclusion on the underlying mechanisms of open-label placebo effects. Moreover, the medical conditions that are studied in this field vary, and little is known about whether open-label instructions can impact itch. The studies described in the current dissertation aimed to investigate whether information provided in an open-label context, modelled after three types of settings in the clinic (see also **Table 1**), could influence the experience of itch in an experimental setting.

In **Chapter 4**, open-label positive suggestions about an itch induction test were compared with neutral instructions. Participants were told that a histamine challenge would elicit little itch in most healthy people, and were given an explanation about how such suggestions may impact experienced itch. This type of information modelling (i.e., providing information about a method that elicits symptoms) has been previously used to test whether (concealed) nocebo or nocebo-like effects can be elicited (see for example, [11,23,25,59]). The study described in **Chapter 4** is, to our knowledge, the first to examine whether this type of modelling could elicit placebo effects in an open-label context. While no direct effects of open-label positive suggestions were found, strong associations between participants' post-suggestions expectations and experienced itch were observed exclusively when open-label suggestions were given. This indicated that participants reported levels of experienced itch close to those that they expected a priori, after open-label suggestions were given. Potentially, giving this type of information, and pointing out the role of expectations in the experience of symptoms, may be helpful when participants or patients already have positive expectations about a treatment. When expectations that patients have prior to treatment are negative however, providing information about the role of these expectations becomes more problematic, as this might only validate that the treatment will likely not work for them. In these cases, interventions aimed at optimizing expectations or at taking away the causes of negative expectations could be more helpful instead. Future research may aim to investigate whether such an approach may be useful to optimize treatment outcomes for itch.

In **Chapters 5 and 6**, positive and negative suggestions were given under open-label conditions as well as closed-label (concealed) conditions. Effects of suggestions on expectations were stronger for the open-label condition, whereas for experienced itch, effects of suggestions under concealed conditions were larger. This apparent contradiction may be explained by the contents of the open-label rationale. In both studies, expectancy is central in the open-label rationale: participants are clearly told that expecting little (or a lot of) itch will influence the intensity of itch that they experience, also when they know about it. This may have primed them to report more profound levels of expected itch when subsequently questioned about their expectations. Regardless of this priming effect however, the studies in **Chapter 5 and 6** show similar patterns in outcomes under both open-label and closed-label contexts. This implies that placebo and nocebo effects occur regardless of whether or not participants were informed about them, and that explicitly informing participants about these effects is not necessarily disadvantageous to clinical

outcomes. However, some caution is needed in drawing this conclusion, as this infers that providing this type of information – that is, explaining the underlying mechanisms of placebo effects – has little actual impact on the formation of expectations about treatment. In **Chapter 5 and 6,** effects of suggestions on expectations were larger in an open-label context however. This suggests that an alternative explanation may be possible: the open-label rationale may have helped in actively shaping placebo and nocebo effects by influencing expectations in a manner that is distinct from concealed placebo and nocebo induction. Speculatively, this would also be in line with previous studies that found that an open-label rationale may (partially) explain placebo effects independently of a previous placebo induction [52,60].

For nocebo effects it is particularly interesting that similar patterns were found for the open-label and closed-label groups. After all, informing patients about nocebo effects has previously been proposed as a potential approach to limit nocebo effects from occurring in clinical practice [61]. This implies that informing about nocebo effects could theoretically have a protective function. However, previous open-label studies [44] show that it does not appear to matter that participants are informed, at least when eliciting placebo effects. This would imply a facilitative (or neutral) role of informing about these effects, which is in contrast with the goal of informing about nocebo effects to prevent them. Findings of the current dissertation likewise support a facilitative (or neutral) role of explaining nocebo effects: the effects of negative suggestions were similar for both open-label and closed-label (concealed) contexts in both **Chapter 5 and 6**. In future research, careful consideration of the manner in which patients or participants can be informed about nocebo effects is necessary, and it should be examined how variations of open-label explanations of nocebo effects may impact the induction of such effects, for example, by comparing different ways of framing this information. It might be especially relevant to examine how variations in explanations of the nature of placebo and nocebo effects in the open-label rationale may impact their effects. Both the current dissertation and previous literature have used an open-label rationale in which an automatic nature for placebo effects is emphasized. While this may be helpful for placebo effects (i.e., they occur regardless of whether you know about them), this may not be the case for nocebo effects. Hypothetically, an explanation of nocebo effects could emphasize active rather than passive components: instead of having these effects be described as automatic responses, focus could be on what can be done about them (e.g., which strategies can be employed to prevent nocebo effects from forming [62-66]). Future research may investigate such strategies.

On a final note, recent findings highlight that open-label placebo effects may depend on a patient's beliefs about placebo effects [47,51]. As described in **Chapter 5**, participants in the open-label groups of this study rated the likelihood that their own experience of itch was influenced by the instructions as rather low. Moreover, effect sizes reported in the current dissertation were generally smaller than in other open-label studies, though this may be due to the other studies being conducted with patient populations rather than healthy volunteers [44]. Future research may aim to investigate for which (patient) subgroups open-label placebos are most likely to be beneficial.

Placebo and nocebo effects in physiological responses to histamine

In line with most previous research [67], no effects of verbal suggestions on physiological responses to histamine were found in the studies described in **Chapter 4, 5 and 6**, with the exception of skin temperature, which changed following suggestions in the study described in **Chapter 5** (i.e., less increase in skin temperature following positive suggestions compared with negative). These findings were not replicated in the study reported in **Chapter 6**, however. It is of note that previous studies found effects of suggestions under hypnosis on skin temperature [68-70]. Moreover, placebo effects have been found for physiological parameters (including skin temperature) that are usually associated with autonomic nervous system (ANS) functioning [71-73]. Indeed, in **Chapter 3**, the only physiological parameter for which group effects were found was heart rate. Any interpretation needs to be made very carefully however, considering that in previous studies suggestions were often made with the intent of changing these parameters (e.g., [68,70]), whereas for the studies in the current dissertation any effect of suggestions (or conditioning) on physiological parameters was treated as a by-product of a placebo response (i.e., the verbal suggestions did not explicitly mention effects on physiological parameters, although effects on other parameters were implied: "you will respond less to the histamine test"). This type of response generalization has been noted before, for example when suggestions of pain were given and skin temperature increased as a results [69], or when suggestions about exaggerated itch following skin prick tests were given and skin reactions were modulated as a result [10].

Generally, placebo and nocebo effects were found more often for subjective symptoms such as itch in the current dissertation, whereas effects on physiological symptoms were more mixed – especially where it concerned placebo and nocebo effects elicited through means

other than conditioning. This is in line with most previous literature and suggests that learning may be necessary in order to facilitate long-term and physiological effects, whereas for subjective symptoms, verbal suggestions may suffice. It has previously been suggested that placebo effects may be elicited by conditioning for unconscious physiological responses, and by expectancy for conscious psychophysiological responses (i.e., pain or itch) [74]. Distinct mechanisms for these effects elicited by conditioning and suggestions have been proposed, but have not been studied extensively so far [19]. For physiological responses to histamine, no comparisons between conditioning and suggestions have been made within a single study so far, which may be remedied in future research.

Limitations

The current dissertation provides novel evidence about placebo and nocebo effect induction for itch and other (psycho)physiological responses to histamine. However, several limitations of the research should be discussed. First, no optimal conditioning protocol could be identified in previous literature (see **Chapter 2**) because the study protocols showed large heterogeneity (related to the specific physiological mechanisms of the used stimuli). This complicated the study design for the study described in **Chapter 3**. It was opted that three acquisition sessions would be sufficient for conditioning to take place. Although stronger learning may occur with an increase of learning trials, gustatory learning is thought to be strongly linked to evolutionary processes and may therefore occur after a single exposure [75]. The decision to measure itch at the end of a three-days evocation phase means that (some) extinction of learned responses could have already occurred. Including histamine tests at earlier time points could potentially have interfered with conditioning effects for other parameters however.

Healthy volunteers were examined in all studies of this dissertation in order to limit the amount of factors that could impact the effects of suggestions and learning on itch. For example, patient groups may have a larger variability in previously learned expectations. These expectations may be especially influenced in patient groups by duration of illness and by previous positive or negative experiences with treatments or the health care system. In addition, by including healthy volunteers only, natural fluctuations in symptom severity or other complications often seen in patient samples were excluded. This may have influenced the study results, as effect sizes could potentially have been smaller due to lower

expected benefit experienced by healthy volunteers. Indeed, participants knew that induced symptoms would be short-term and that they would be able to stop the induction of symptoms at any point in time. This considerably lowers benefits of participating in a study, and patient samples may arguably have a higher wish or desire for improvements in their symptoms, especially when complaints are chronic. Future research may therefore consider investigating placebo and nocebo effects in patient populations for whom itch is a relevant symptom, as placebo and nocebo effects may be more impactful there.

The studies in which suggestions about itch were given were mostly proof of concept studies, in which especially new open-label instructions were tested. Comparisons with previous open-label studies were made in the current dissertation, but some caution is needed, especially given that the content of the rationale differs across studies. For example, it was not possible to use one of the key arguments in previous open-label rationales (i.e., that placebo effects are learned) for the studies described in **Chapter 4-6.** Given that verbal suggestions were used to elicit placebo and nocebo effects**,** together with instruments (e.g., tonic, transdermal caffeine patch) unlikely to have been associated with itch treatment in the past, providing a rationale about learned placebo effects would have been redundant – learning was simply not relevant for the studies described in **Chapter 4-6** and the studies show that open-label effects may also occur without mentioning that placebo effects are learned. However, interpretations need to be made carefully, as demand characteristics may play a role in such studies. The findings of the current studies should therefore be confirmed by future studies, preferably with a double-blind study design. Moreover, future research may consider including a neutral control group, as in the current dissertation positive and negative suggestions were often compared. While this does allow for assessment of the impact of suggestions on itch and other parameters, no estimation of the 'true placebo effect' or the 'true nocebo effect' can be made, as the normal course of repeated tests is unknown.

Finally, limitations concern the power calculations for the secondary hypotheses in the studies described in this dissertation. The effect sizes used as input for these calculations were derived from previous work on placebo and nocebo effects in itch, and resulted in a sample size adequate to test group differences under the separate open-label and closed-label contexts. However, analyses for the secondary outcome measures, such as wellbeing, self-rated and physical skin response to histamine (**Chapter 3-6**), and heart rate, skin conductance, and pulmonary functioning (**Chapter 3**), may have been underpowered. Likewise, limited power may explain why little evidence was found for the moderating role

of personality traits, for example, optimism or neuroticism. Previous work shows indications that personality traits like these may be related to placebo and nocebo responding [10,76,77], but this was not confirmed by the studies described in the current dissertation.

Future research directions

The current dissertation raises several relevant questions that may be further investigated in future research. First, as demonstrated in the systematic review, the field of classical conditioning of immune responses relevant to dermatology has been investigated extensively with animal models. Human trials have focused most on conditioned exacerbation of allergic symptoms, whereas comparatively little is known about how to use classical conditioning mechanisms to enhance treatment efficacy. At the moment, only two studies focused on suppression of allergic symptoms using conditioning mechanisms, but these were unable to distinguish between conditioning and expectancy effects for subjective symptoms. The study described in **Chapter 3** extends these findings by investigating pharmacological conditioning of antihistamine in healthy volunteers. It was demonstrated that conditioning marginally improved itch in response to a histamine challenge. Theoretical implications from this study are that classical conditioning indeed may result in learned suppression of itch or other markers of allergic symptoms, but that, hypothetically, conscious learning (i.e., experiencing reduced symptoms during acquisition) may strengthen these effects. Therefore, effects may be stronger in case of patient studies, as patients could rapidly notice changes in their symptoms, whereas for studies with healthy volunteers, symptoms first need to be deliberately induced. As a first step however, future research may consider strengthening the design used to test pharmacological conditioning with H1-antihistamines. For example, future research may consider including multiple histamine tests, especially given that the timing of conditioned responses for itch, and specifically antipruritic conditioning with antihistamines, has not been investigated systematically. Moreover, including histamine tests in the acquisition phase may help strengthen associative learning for itch in healthy volunteers. It could be possible that in the current, study participants may not have noticed effects of the medication, which would set them up for insufficient learning of associations between CS and UCS. Including multiple tests, or including patients who experience symptoms during acquisition for which they can notice improvements, would help strengthen this type of associative learning. Alternatively,

other outcome parameters could be considered in the future, for example, measuring immune markers related specifically to antihistamine in the blood (e.g., interleukins) [78,79]. These parameters may potentially be more sensitive to relatively smaller conditioned effects compared to subjective or clinical parameters (e.g., itch, pulmonary functioning), but were not measured in the current study.

The conditioning study described in **Chapter 3** showed that conditioning marginally reduced itch for both open-label and closed-label contexts. This raises the question whether deception is necessary for conditioning to occur. Potentially, the conditioning procedure may be explained to participants without losing effects for itch. This needs support of future research, however, as conditioned effects in the current study were marginal and not significant, which hampered assessment of the impact of the open-label rationale. It would be relevant for future studies to further focus on whether and under which circumstances open-label conditioning could reduce itch, as non-deceptive placebo induction may be promising to apply in clinical practice. Regarding open-label placebo effects, another interesting question was raised in **Chapter 4**. It was demonstrated that instructions about low itch and about how participants' expectations impact itch experience led to higher positive associations between expected and experienced itch. However, emphasizing such a relation between expectations and symptomatology may become problematic for nocebo effects, specifically in populations-at-risk, for example, individuals who are highly anxious about receiving medical treatment or have a high fear of side effects. The impact of negative information in these subpopulations may be investigated more thoroughly in future research, for example, by comparing the effects of such instructions across groups with high or low fear of side effects.

Future research may also consider investigating effects of learning and instructions on scratching or other behaviors related to itch. In the systematic literature search in **Chapter 2**, studies are described that show that social cues can impact not only itch (i.e., contagious itch) but also the frequency of spontaneous scratching behavior [80-82]. Scratching has been found to exacerbate itch in skin conditions, and to result in a vicious itch-scratch cycle that can lead to significant impairments for patients (e.g., loss of control, feelings of shame, social isolation) [83]. Therefore, investigating whether placebo and nocebo effects can significantly influence scratching behavior may be a worthwhile approach for future research. So far, a single study investigated whether nocebo effects could generalize from itch to scratching in healthy volunteers, and found no evidence for such response generalization [84]. Future research may investigate whether the elicitation of placebo

effects for itch can also result in reduction of scratching behavior (i.e., response generalization). If it can be demonstrated that placebo effects can generalize from itch to scratching behaviour, this may lead towards new therapeutic possibilities that could target, for example, the itch-scratch cycle.

Finally, the studies described in **Chapter 5 and 6** show that placebo and nocebo effects elicited by verbal suggestions are similar across open-label and closed-label contexts. This raises another theoretical question on the similarity of such open-label and closed-label placebo and nocebo effects. In these chapters, the open-label rationale was provided as an add-on for verbal suggestions about a treatment tool (tonic or caffeine patch). In general, the elicited effects were similar under open-label and closed-label conditions, which has some important implications for research. Careful consideration of the type of information to be provided is necessary. Moreover, the goal that is to be achieved by providing information needs to be considered: if the intention is, for instance, to prevent side effects from occurring, it may not be sufficient to only explain that negative expectations can result in nocebo effects. Hypothetically, such a method could just as likely facilitate nocebo effects (especially when the information about nocebo effects is negatively framed). Rather than explaining that nocebo effects occur through conditioning as a passive, automatic process, it may be more beneficial instead to explain that expectations can be actively used to modulate experience of symptoms [62-66]. Future research could examine whether such an approach can be used to prevent nocebo effects, as well as how this would relate to placebo effects. For instance, it may be worthwhile to investigate whether an open-label rationale that promotes empowerment and active modulation of expectations can enhance placebo effects, or whether it is more prudent for open-label placebo effects to emphasize automaticity of learned responses.

Implications for clinical practice

The results of the current dissertation show that placebo and nocebo effects can be induced for itch and itch-related conditions and symptoms of the mucous membranes using a multitude of methods, including verbal suggestions and conditioning. The information this provides may be used to enhance patients' expectations regarding treatment outcomes in clinical practice, for example, by emphasizing positive information when explaining to-be-expected treatment outcomes to patients and by positive framing of potential adverse effects. For example, when explaining side effects occurrence, it may be useful to discuss

the percentage of people that *do not* experience them rather than the percentage that do [34-38], or to change the manner of informing about side effects of a treatment (e.g., fostering a mindset that side effects may signal that therapies such as immunotherapy work; [85]). Moreover, conditioning mechanisms could be used to maximize placebo effects. For example, by varying the doses of medication, without changing any of the attributes (e.g., the amount, color and shape of pills), conditioned effects could be used to potentially achieve similarly or more effective treatment with lower doses of medication. Several studies already show that this method of conditioned dose reduction can lower medication intake without loss of treatment efficacy for various medical and psychological conditions [5,56]. Findings of the study described in **Chapter 3** indicate that such an approach may potentially be useful to support pharmacological treatment of itch-related conditions as well, however, this needs to be investigated more thoroughly before it can be applied in clinical practice.

In **Chapter 4**, it is demonstrated that open-label positive suggestions about an itch-inducing method can result in positive outcome expectations, and that these in turn are associated with lower itch experience during an experimental itch induction test. This shows that it may be relevant to consider in which ways potentially unpleasant tests and proceedings in health care settings are introduced to patients. Though more research is needed, these findings provide a first indication that it may be helpful to address patients' own expectations and to discuss the impact that these expectations could have on, for example, recovery from medical proceedings, or pain levels during such procedures, especially when patients are highly anxious for invasive procedures. To illustrate, there are studies that show that communication interventions, informational preparation and positive suggestions can influence pain levels [86]. This could potentially be the case for itch as well. Moreover, next to negative emotions (e.g., stress and anxiety), high levels of ruminating (as a chronic negative expectation) have been found to be a predictor for itch in clinical settings as well [87-89]. The findings described in **Chapter 4-6** show that suggestions can impact itch experience, and suggest that providing information about placebo (and nocebo) effects could be a useful way to enhance expectancy effects for itch. In clinical practice this may translate, for example, to psychoeducation regarding the role that expectancy has in harnessing placebo effects for somatic symptoms. Finally, the current studies give some indications that open-label conditioning may potentially be a worthwhile method to facilitate the use of placebo effect mechanisms in clinical practice. If this can be replicated and extended by future research (e.g., with different conditioning paradigms or patient

populations), this may then translate into therapies that utilize conditioned dose reduction in an open-label context. Conditioned dose reduction has already been found effective in psoriasis in a closed-label (i.e., concealed) context [5]. If it is proven effective in an open-label context, medication use could be reduced, and the full potential benefits of placebo effect mechanisms could be reaped in clinical practice as a result.

Conclusion

In the current dissertation, we investigated the experimental elicitation of placebo and nocebo effects for histamine-induced itch and other psychophysiological responses to histamine. Placebo and nocebo effects were examined in a systematic review of the literature, as well as in a series of studies that used multiple induction methods (i.e., classical conditioning, verbal suggestions) for placebo and nocebo effects under both open-label and closed-label (i.e. non-concealed and concealed) conditions. Overall, the dissertation demonstrates that placebo and nocebo effects can be elicited for itch and itch-related parameters by several means. It is shown that histamine-induced itch may be influenced by suggestions under both open-label and closed-label conditions. Moreover, the dissertation shows that potentially, antipruritic effects of antihistamines may be sensitive to conditioning to some extent, though this needs to be investigated further in future research. Placebo (and nocebo) effects can be elicited by conditioning and suggestions with participants' knowledge as well, which is a first step in opening new pathways towards therapeutically applying placebo and nocebo effect knowledge without deception or concealment of methods. Using associative and instructional learning in medical treatments with participants' knowledge may be a promising strategy to maximize placebo effects, minimize nocebo effects, and help in reducing medication use for (chronic) itch and other somatic complaints.

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