Placebo and nocebo effects on itch: An experimental approach

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CHAPTER 7

SUMMARY & GENERAL DISCUSSION

SUMMARY

Placebo and nocebo effects are positive or negative treatment effects respectively, unrelated to the treatment mechanism, which are induced by patients' expectations (1-3). Placebo and nocebo effects are known to play a role in treatment effects for various symptoms and conditions, especially in the field of pain. The aim of the current disseration was to increase understanding of placebo and nocebo effects on itch.

In **Chapter 2**, we provided a state of the art overview of the empirical literature on the role of placebo and nocebo effects on itch and their predictors with regard to individual characteristics. Besides, these findings were compared to what is known in the field of pain. We showed that expectancy learning via verbal suggestion and conditioning can induce placebo and nocebo effects on itch, by which the combination of both procedures seems most promising (see Chapter 3). Furthermore, itch can also be induced 'contagiously' in which expectations seem to play a role. This is unique for itch, and does not occur to a similar extent for pain. Regarding predictors of placebo and nocebo effects on itch and contagious itch, preliminary evidence proposes a role for individual psychological characteristics and personality traits related to negative outcome expectancies, such as neuroticism, anxiety, depression or worrying, however results are mixed. So far, no conclusive predictors for placebo and nocebo effects on itch were found.

In **Chapter 3**, we experimentally studied the effects of expectancy learning via verbal suggestion, conditioning and the combination of both to induce placebo and nocebo effects on electrically induced itch in healthy participants. This study showed that significant placebo and nocebo effects were induced when combined procedures of conditioning and verbal suggestion were applied when compared to a control procedure. The conditioning and verbal suggestion procedures applied individually did not result in significant placebo and nocebo effects in comparison with the control procedure. These results are in line with research on pain and other physical sensations like fatigue or nausea, which has in general shown that largest placebo and nocebo effects are obtained when verbal suggestion is combined with conditioning. Furthermore, we found indications that individual characteristics related to negative outcome expectancies, i.e., more worrying, higher negative affect, less hope and

lower levels of extraversion, were associated with greater nocebo responses, whereas only a significant correlation was found for the magnitude of placebo effects with less hope.

In **Chapter 4**, we investigated whether it was possible to reverse previously established nocebo effects on itch. To this end, we first induced nocebo effects regarding electrically evoked itch in healthy participants using conditioning with verbal suggestion. Subsequently, to reduce the nocebo effects, positive expectations were induced by conditioning with verbal suggestion (counterconditioning), while in the control conditions, either negative expectations were continuously induced or an extinction procedure was applied. Results showed that the counterconditioning caused reduced nocebo effects on itch in comparison to the control conditions. Moreover, nocebo effects were reversed, indicating a placebo effect. We also found indications that the reduction in nocebo effects regarding the electrical stimulation generalized to reduced itch evoked by histamine iontophoresis. Individual characteristics did not appear to be associated with the observed effects. This study indicates that learning via counterconditioning with verbal suggestion seems a promising strategy to diminish nocebo effects on itch.

In **Chapter 5**, we investigated whether nocebo effects and reversed nocebo effects on electrically induced itch (see Chapter 4) generalize to scratching behavior. This experimental study showed that participants tend to scratch more when itch stimuli of a higher intensity are applied than when itch stimuli of a lower intensity are applied. However, no significant nocebo effects or reversed nocebo effects were found on scratching, apart from some indirect indications. These findings suggest that despite the close link between itch and scratching, generalization of nocebo effects from itch to scratching does not inevitably occur. This could possibly depend, among others, on the intensity of experienced itch or the specificity of the verbal suggestion, which only targeted itch; no additional verbal suggestion regarding scratching was provided.

In **Chapter 6**, we explored the role of participants' existing itch-related memories and expectations - or cognitive schemas - in placebo and nocebo itch responding. To this end, specificity and valance of memories and expectations for itch were assessed in healthy participants prior to a placebo and nocebo experiment on itch. Results indicated that participants who were more specific in their itch-related memories and who had less negative itch-related expectations for the future were more likely to be placebo responders. No

significant differences in cognitive schemas were found between the nocebo responders and nonresponders. Cognitive schemas of itch related memory and expectations could be promising in explaining interindividual differences in placebo itch responding.

Taken together, the results of the studies presented in this thesis further underline that placebo and nocebo effects play a role in itch perception. We found that itch is highly susceptible to suggestions and placebo and nocebo effects can be induced on itch by verbal suggestion and conditioning. Most notably, our findings show for the first time that particularly the combination of conditioning with verbal suggestion is most promising for inducing both placebo and nocebo effects on itch, which is in accordance with placebo research on pain. Moreover, a new and promising finding is that counterconditioning has shown to reverse nocebo effects on itch. Future research may build upon the findings of this thesis to further enlarge our knowledge on placebo and nocebo effects on itch and how to maximize or minimize them, respectively, also in a clinical setting, to eventually optimize available interventions for patients suffering from chronic itch.

GENERAL DISCUSSION

The main aim of this thesis was to provide insight into the role of expectancy learning in placebo and nocebo effects on itch. More specifically, we studied the effectiveness of the different expectation inductions of verbal suggestion and conditioning on experimentally induced itch in healthy individuals. We also investigated how nocebo effects on itch can be reduced. Moreover, we explored if induced nocebo and placebo effects on itch generalize to other itch stimuli and scratching behavior. Additionally, we explored the role of individual psychological characteristics involved in placebo and nocebo responding. In this final chapter, we summarize and discuss the main findings presented in this thesis. We will address limitations, discuss the implications of the findings, and we present directions for future studies.

Learning mechanisms in placebo and nocebo effects on itch

In the current thesis we particularly investigated the effects of two methods of inducing placebo and nocebo effects on itch and reducing nocebo effects on itch (Chapter 3 & 4). Specifically, we investigated placebo and nocebo effects induced by verbal suggestion and conditioning, as well as the combination of these expectation inductions. Moreover, the combination of verbal suggestion and conditioning was used to reverse established nocebo effects on itch.

Verbal suggestion

Our experiment as described in Chapter 3 investigating whether verbal suggestion and/or conditioning could induce placebo and nocebo effects on itch did not show that placebo or nocebo effects can be induced by verbal suggestions alone. More specifically, verbal suggestion elicited a marginally significant nocebo effect on itch in comparison with a control procedure in the testing phase. However indirectly, significant nocebo effects were induced in the learning phase of the verbal suggestion group, in which the procedure is exactly the same as in the testing phase. So, perhaps the nocebo effects were already partly extinguished in the testing phase. In addition, no significant placebo effects were induced by verbal suggestion when compared with the control group, although the verbal suggestions

resulted in significantly lower levels of itch in the testing phase for the itch stimuli associated with the placebo cues versus the neutral cues (within-subjects effect).

Our results pertaining verbal suggestions are overall in line with other studies conducted on placebo- and nocebo-(like) effects on itch. With regard to placebo effects, only Darragh and colleagues (4) were successful in reducing reported itch sensations during a histamine skin prick procedure, using only verbal suggestion regarding the effects of an inert placebo cream. One study on histamine iontophoresis provided indirect evidence for induction of placebo effects on itch by verbal suggestion (5), but other studies failed to induce placebo effects using verbal suggestions (6-9). These mixed results indicate that more research is needed to understand under which circumstances verbal suggestions can induce placebo effects on itch. With regard to nocebo effects on itch, apart from our experiment, only nocebo-like effects were previously described since the verbal suggestion in former studies were not attributed to a certain inert (nocebo) stimulus like an electrode or pill (7, 10, 11). Altogether these studies showed that the experience of itch can be aggravated by verbal suggestions. Moreover, as demonstrated by contagious itch research, itch seems highly susceptible to suggestion and can be aggravated by audiovisual stimuli (12). In our experiment described in Chapter 3, we used two phases (learning phase for the conditioning procedures and testing phase to test for nocebo (and placebo) effects). This has probably led to extinction of effects that were present in the first (learning) phase, whereas to test for effects of verbal suggestion one single phase is sufficient (13). It can be concluded that verbal suggestions can alter the experience of itch, although results are mixed and not robust. This might imply that using verbal suggestions for itch may be effective only under certain circumstances, for example depending on the amount of testing trials or characteristics of the verbal suggestion, and for a limited duration.

Conditioning

Previous research in for example pain showed that conditioning is an effective and robust way to induce placebo and nocebo effects. However, most of these studies combined conditioning with verbal suggestions. We were the first to investigate the role of conditioning - without verbal suggestion - in placebo and nocebo effects on itch (Chapter 3). Results of our experiment showed that solely conditioning did not elicit significant nocebo or placebo effects on itch when compared to a control procedure. The few studies on pain, investigating conditioning without verbal suggestion, yielded mixed results (14-19). Generally, in these

studies significant nocebo or placebo effects were found when more or longer lasting learning trials were used (15-19). It is known from the conditioning literature that conditioned effects are stronger when more pairings of the conditioned stimulus (CS) and unconditioned stimulus (US) are applied. Additional experience with repeated CS – US trials provides the opportunity to obtain more information about the relationship between stimuli through contingency learning (20). When using more or longer conditioning trials, the learned association may become more predictable. It could be that the exposure to the paired CS – US trials in our experiment was not sufficient to result in associations about the causal relationship between the placebo/ nocebo stimuli and low and high intensity itch stimuli.

Combination of conditioning and verbal suggestion

Although we found in our experiment that neither verbal suggestion nor conditioning alone did result in significant placebo or nocebo effects on itch (see previous paragraphs), combining both procedures led to significant and robust placebo and nocebo effects on itch (Chapter 3). Because of the successful induction of placebo and nocebo effects on itch by the combination of conditioning and verbal suggestion in that study, we decided to also use this combined procedure for our subsequent experiment in which we wanted to induce nocebo effects as baseline (Chapter 4). Again in this experiment, significant nocebo effects on itch were induced when conditioning and verbal suggestion were combined. These results are consistent with findings of subsequent studies in healthy participants (21), but even so in patients with atopic dermatitis (22). Especially for itch, which seems highly susceptible to external cues (12), adding verbal suggestions to the conditioning procedure might facilitate the induction of placebo and nocebo effects. That placebo and nocebo on itch are most effectively induced with a combination of both conditioning and verbal suggestion is also in line with placebo and nocebo research in for example pain (13, 23, 24). Combining different methods to induce expectations, each activating different learning processes (i.e., conditioning and instructional learning), seems especially effective (25). Conditioning can shape both automatic and conscious expectations about a given cue (26) and the addition of verbal suggestions might reinforce the learning. However, so far studies exploring the possible additive and interactive effects when aiming at multiple learning processes in itch or pain remain limited and more research into the comparative and combined effects of different expectation inductions is necessary.

Reversing nocebo effects on itch

Due to the major impact of nocebo effects in clinical practice, researchers increasingly hint at examining ways to minimize nocebo effects to improve clinical outcomes. In this thesis, we showed that nocebo effects on itch can be experimentally reduced by counterconditioning (Chapter 4). After initially inducing nocebo effects on itch at baseline, positive (placebo) expectations were induced to counteract nocebo effects (Chapter 4). We found that nocebo effects on itch can be reduced by this positive expectation induction consisting of a combined conditioning and verbal suggestion procedure. Moreover, nocebo effects were even reversed after counterconditioning, demonstrating significant placebo effects. This finding extends results of a study on nocebo-like effects regarding health effects of wind turbine sound induced by verbal suggestions (27). Crichton and colleagues showed that positively framed information regarding health effects of wind turbine sound can dilute or even reverse the effects of negative expectations (27). Furthermore, the successful reversal of nocebo effects on itch when using counterconditioning is consistent with a large body of research showing that counterconditioning can effectively change learned behavior in, for example, fear and evaluative conditioning paradigms (28). The results of the study described in Chapter 4 that also nocebo effects on itch can be changed through counterconditioning, suggests that learning via counterconditioning and verbal suggestion might represent a promising strategy to diminish nocebo effects on itch in clinical practice.

Generalization of placebo and nocebo effects on itch to another itch stimulus and scratching

The studies presented in the current thesis indicate that generalization might play a role in placebo and nocebo effects on itch. In Chapter 4 we found that reduced nocebo effects regarding electrically evoked itch generalized to a different itch stimulus, namely histamine iontophoresis. This is in line with previous research on generalization showing that placebo and nocebo effects can generalize to novel but related stimuli (29, 30). We did not find direct support for generalization of nocebo effects on itch to a different modality, namely scratching. This is contrary to previous related studies on contagious itch, showing that expectation inductions addressing itch can also influence scratching behavior of participants (12). More research into generalization of placebo and nocebo effects on itch is needed since generalization can possibly explain placebo and nocebo effects occurring in unconditioned,

but related situations (such as new itch medication, a new physician or hospital setting), and can possibly transfer to different symptoms.

Individual differences

There is a substantial interindividual variability in placebo and nocebo effects, which may partly be related to individual characteristics like personality traits (31, 32). In the different experiments of this thesis, we explored several individual characteristics regarding personality traits and affective states in relation to placebo and nocebo responding on itch as well as counterconditioning of nocebo effects on itch (Chapters 3, 4 and 6). Although we found some indications for worrying, negative affect, hope, and extraversion to be associated with nocebo effects on itch, none of the characteristics stood out and replicably demonstrated to play a role in placebo or nocebo responding on itch. Our results are generally in line with first indications from studies on contagious itch that suggest a relationship between higher levels of contagious itch and negative mood (33, 34) as well as neuroticism (35). However, more research with sufficient power is required to support the consistency and validity of these findings. Also in the field of pain, there is a lack of systematic research in individual characteristics predicting placebo and nocebo responses (31, 36). Possibly, interactions between individual characteristics and situational factors like the targeted symptom or method of expectation induction play a role. For example, a recent study in conditioned placebo effects on pain, investigating the role of verbally induced expectations and frequently reported predictive characteristics (i.e., dispositional optimism, anxiety state, and gender), has demonstrated that placebo effects were not only influenced by expectancy levels (verbal suggestions concerning no, low or high expectations for pain reduction) or individual characteristics alone, but also depended on their interactions (37). For example, participants who were more optimistic showed greater placebo effects, but only in the low expectancy group and not in the high expectancy group (37). Furthermore, the role of biomarkers such as genetic predispositions in relation to placebo and nocebo effects on itch could be investigated, given their potentially predictive value in placebo or nocebo effects on pain (38-40).

Given the relevance of previous experiences and related memories in the formation of expectations, in Chapter 6 the role of cognitive schemas (i.e., mental structure in which thoughts, information, and their inter-relationships are categorized) of memories about the

past and expectations about the future was tested in placebo and nocebo responding on itch with a method adjusted from the pain literature (41-43). Findings showed that placebo responders retrieved more specific memories of itch-related events and endorsed fewer negative itch-related expectations for the future than did the placebo nonresponders. No differences in cognitive schemas were found between nocebo responders and nocebo nonresponders. This is the first study on placebo and nocebo effects with this unique approach, which was inspired by previous research in the field of psychopathology indicating that reduced specificity of memories is related to several negative outcomes such as depression, trauma-related psychopathology and difficulties in problem solving (44, 45). Although cognitive schemas do not seem to explain a large part of placebo and nocebo responding, it is a promising target that demands further study in relation to placebo and nocebo effects.

Limitations

The research presented in this thesis should be regarded in the light of certain limitations. Limitations concerning external validity are discussed first. To begin with, the study population in this thesis included healthy participants only. Although it is important to study mechanisms underlying placebo and nocebo effects as well as the minimization of nocebo effects in a healthy state, findings are not directly generalizable to clinical contexts for the following reasons. Patients might respond differently to itch stimuli and expectation inductions than healthy participants. For instance, a recent review and meta-analysis by van Laarhoven and colleagues (46) showed that patients react differently to itch stimuli, and more strongly on lesional skin in particular, than healthy participants. Sensitization processes are likely to be involved (46, 47). Moreover, patients might respond differently to placebo and nocebo manipulations than healthy participants. For example greater motivation for itch relief, previous negative experiences with regard to treatments, or anxiety may play a larger role in patients than in healthy participants (24, 48, 49). A study in contagious itch showed that patients with atopic dermatitis (AD) are more susceptible to contagious itch cues than healthy individuals (34). With regard to pain, a meta-analysis showed that the magnitude of placebo effects is higher in patients than in healthy individuals (48). This indicates that findings from studies in healthy individuals possibly underestimate the magnitude of placebo effects

in patients (48). However, within-study comparisons do not suggest differences in placebo effects on pain between patients and healthy individuals (24, 50). Future studies should directly compare the effects of placebo and nocebo manipulations regarding itch stimuli between healthy participants and patient samples.

Second, we used short-lasting experimental itch stimuli of moderate intensity in artificial laboratory settings that cannot directly be generalized to itch sensations in daily life (51). Itch in daily life is often more intense, longer lasting and unpredictable, especially in individuals suffering from chronic itch (52). For example, it is not unlikely that nocebo effects are more robustly present in patients that suffer from chronic itch, for instance due to their negative cognitive schemas regarding the itch (Chapter 6), and might therefore be harder to reduce.

Furthermore we would like to address some important limitations that concern methodological issues. First, participants tended to report decreasing levels of itch as the experiment progressed, probably because they habituated to the stimulation (53-55). This may have influenced the main findings on nocebo and placebo effects on itch in particular because a test phase was always at the end of the experimental session (Chapters 3 and 4). Moreover, it could be that the decline in itch resulted in less often reaching the participants' scratch threshold (56), which could have influenced the scratching results, also mainly in the test phase of the experiment (Chapter 6). However, since the studies were aimed at investigating the effect of learning by conditioning, repeated itch stimulations were required and the long duration could not be avoided. Moreover, even though some participants experienced hardly any itch at the end of the experiment, sensitivity analysis showed that this did not affect the main results on placebo and nocebo effects.

Second, blinding was not always fully possible because of the nature of the studies. It was infeasible to blind the experimenter for the conditions due to the different verbal suggestions the experimenter had to provide to the participants in the different groups. This might have led to observer or performance biases. However, we tried to maximize blinding on all other facets by e.g., not notifying participants about the presence of different groups, by randomizing the stimulus order automatically within the stimulation control, and by blinding the independent raters of scratching behavior for the conditions. It can also not be excluded that participants responded in a way that they thought was expected from them, for example because they knew the goal of the study or formed their own hypotheses about the study

aims (i.e., socially desirable responding; (57)). This is however not very likely, since we assessed participants' thoughts about the goal of the studies and hardly any participants were aware of the true research aims.

Third, assessing placebo and nocebo effects by self-reported measures can be susceptible to response bias like social desirability (57). Although the involvement of response bias cannot be factored out and might even be inherent to studying placebo and nocebo effects on subjective outcomes (57, 58), additional objective outcomes can be valuable, like automatic behavior (e.g., scratching behavior) or neuroimaging outcome measures using functional magnetic resonance (fMRI) or positron emission tomography (PET) (59).

Last, we did not assess explicit expectations participants had about the itch stimuli because this could have affected the course of the experiment and results (e.g., demand effects). This also implies that it remains uncertain if the placebo and nocebo effects found in the present study are accountable to explicit expectations (25). A number of recent studies indicate that placebo and nocebo effects can arise without the mediation of explicit expectations, in pain among others (e.g., (16, 17, 60)). With regard to itch, more research into the underling mediating mechanisms of placebo and nocebo effects is needed.

Future research directions

Our studies were aimed at providing insight into the mechanisms underlying placebo and nocebo effects on itch. We showed that placebo and nocebo effects can be experimentally induced by the combination of conditioning and verbal suggestion and we have shown that nocebo effects on itch can also be reversed. Based on these results, recommendations for future research can be formulated. Since this area of research is still very immature, there is a clear need for future studies to continue to investigate the mechanisms underlying placebo and nocebo effects on itch.

First of all, further research into the different expectation inductions with regard to placebo and nocebo effects on itch is needed. With regard to pain, evidence for the role of verbal suggestion and conditioning is robust (61, 62). However with regard to itch, replication studies are warranted to verify the previously found effects of conditioning and verbal suggestion on placebo and nocebo effects (Chapters 2, 3 & 4). Furthermore, conditioning

methods could also be used to reduce reliance on medication or medication side effects. For example, in the treatment of psoriasis it was demonstrated that after a baseline conditioning period with medication (100% of drug dosage on all days) a placebo-controlled dose reduction treatment schedule (100% of drug dosage provided on 25 – 50% of the days, placebo on other days) resulted in greater skin lesion reduction than in the group whose treatment dose was simply reduced (25 – 50% of drug dosage on all days). Moreover the dose-reduction schedule was as efficient as the full dose treatment group (100% of drug dosage provided on all days) (63). Future studies should investigate the applicability of these dose-extending placebos in dermatological treatments. Additionally, observational learning might be another interesting expectation induction to explore regarding placebo and nocebo effects on itch (51). In pain, observational learning has shown to yield effects of comparable strength to those of conditioning with verbal suggestion methods (64-66). Nocebo effects on itch might especially be subjective to observational learning due to the contagious nature of itch as described in studies on contagious itch (Chapter 2) (12, 67). Future studies might investigate these expectation inductions separately and also assess the effects of the combination of conditioning, verbal suggestions, and observational learning on placebo and nocebo effects on itch.

Second, placebo and nocebo effects on itch could be investigated regarding different human experimental models of itch to study different itch sensations and itch pathways that are relevant for different types of pruritus seen in clinical practice (51, 68). Electrically evoked itch as used in our studies (Chapters 3, 4, & 5) produces a different sensation of itch than for example histamine- or cowhage-evoked itch. Cowhage-evoked itch might provide a model that closely resembles itch experienced by patients with, for instance, AD (51, 68). Additionally, histamine-evoked itch is mediated through histaminergic pathways, which can resemble itch seen in allergy and urticaria (68). Future studies could explore whether conditioning with cowhage- or histamine-evoked itch has potential, and test whether the effects on conditioning and counterconditioning as demonstrated in the current thesis are valid for different experimental models of itch.

Third, future research might focus on placebo and nocebo inductions directly targeting scratching behavior. In Chapter 5, we explored the generalization from nocebo - and reversed nocebo - effects from itch to scratching. Where the expectation induction merely aimed at

itch, we wanted to assess whether effects on itch generalized to scratching behavior. Although we were unable to obtain nocebo effects on scratching behavior within the used design, considering the important role of scratching in the maintenance and exacerbation of itch and skin conditions (69, 70), future studies could attempt to directly target placebo and nocebo effects on scratching behavior.

Fourth, future research could further investigate determinants of placebo and nocebo effects on itch, including individual characteristics. Our review (Chapter 2) and experimental studies as described in Chapter 3 & 6 have provided some preliminary indications for a possible role of characteristics like anxiety, worrying and specificity of itch related memories and expectations in placebo and nocebo effects on itch. However, research is very limited and results are not consistent. Future research should thoroughly investigate which individual characteristics may predict placebo and nocebo effects on itch, like personality characteristics (Chapter 2 & 3) and genetic predispositions (38). For example, in pain research specific genotypes or combinations of genotypes (such as COMT haplotypes) have been shown to predict placebo responding (71). However, individual characteristics like personality or genetic variances can only partly explain placebo responding and interactions with situational factors like method of expectation induction are of importance (37, 71). With regard to itch, it might be of great value to look into the interactions of individual characteristics and different methods of expectation inductions that determine the magnitude of placebo and nocebo effects. By tailoring the way a treatment is provided or framed (with verbal suggestions) such that it matches the individual patient's style, we can possibly enhance placebo effects and minimize nocebo effects in the clinical setting, and therewith reduce patients' burden.

Fifth, we recommend future studies to further investigate neurobiological mechanisms in placebo and nocebo effects on itch. Extensive neurobiological research, predominately in pain, indicates that placebo and nocebo effects are characterized by changes in brain processes (72-74). With regard to itch, so far only two neuroimaging studies on nocebo effects have been published (21, 22) and three on contagious itch (35, 75, 76); all providing mixed evidence for involved brain processes. Furthermore, these studies report different activated brain areas between patients and healthy individuals (21, 22, 35, 75, 76). Possibly, nocebo effects on itch are processed differently in patients with chronic itch than in healthy individuals (76). Additional research with neuroimaging of placebo and nocebo effects on itch is clearly

warranted. Additionally, tracking brain processes during counterconditioning with verbal suggestion might also provide new insights and better understanding of the neurobiological mechanisms of reversion of nocebo effects on itch, which may contribute to advancing treatment effects for chronic itch.

Sixth, future research should aim to replicate our results in patient groups. As a first step, lab studies could be conducted using experimentally evoked itch to investigate the effects of verbal suggestion and conditioning, and potentially observational learning, on placebo and nocebo effects on itch and scratching in patients with chronic itch. Moreover, it is worthwhile to investigate the reversibility of nocebo effects on itch in patient groups, both on temporarily induced nocebo effects and nocebo effects that were acquired by experiencing clinical itch. Findings from such studies could facilitate the translation of placebo effects to clinical settings to integrate expectancy learning in treatments for itch and screen for patients who show nocebo effects or are high at risk for nocebo effects. How to maximize the clinical utility of placebos will be discussed in the next paragraph.

Seventh, placebo interventions are usually administered in a deceptive way, which leads to ethical issues for clinical practice. Open-label placebo studies avoid this by openly informing participants that they receive a placebo and educate them about placebo effects (77). With regard to itch, some initial studies on verbal suggestion and on conditioning indicated a potential role for open label placebo (5, 6, 78). Future research could further optimize these methods and investigate under which circumstances open label placebo can be successful in reducing itch.

Finally, next to these recommendations concerning itch, there is a clear opportunity for future research to further investigate the reversibility of nocebo effects in different sensations and conditions, like in pain. Directly comparing counterconditioning of nocebo effects on itch and e.g., pain provides more insight into general and specific underlying mechanisms. Moreover, future studies should explore whether counterconditioning with verbal suggestion could provide a promising strategy to reduce nocebo effects for other sensations as well and enhance treatment effects across different symptoms and conditions.

Clinical implications

The results of the present thesis indicate that placebo and nocebo effects play an important role in the experience of itch. Although further empirical support is required and the studies described in this thesis concern experimental research in healthy individuals, some tentative implications can be drawn based on the current results and literature.

First, findings from our review and experimental studies suggest that placebo and nocebo effects on itch can be induced by a combination of verbal suggestion and conditioning (Chapters 2, 3 & 4) and possibly also by verbal suggestion alone (Chapter 2 & 3). These results underline the importance of taking into account patients' previous experiences with itch treatments. Moreover, this emphasizes the importance of how information about a certain treatment for itch is provided, for instance by clinicians. Clinicians should pay attention to always informing patients about the intended beneficial treatment effects and provide realistic information about the expected outcomes (79). This does not only lead to short-term positive effects, repeated positive experiences with a treatment may eventually lead to longer lasting placebo effects due to conditioning (80, 81). Additionally, information about negative side effects should carefully be provided. To minimize nocebo effects, side effects could positively be framed, e.g., "70% will not experience itch" (82), patients could be informed about how nocebo effects can play a role in their treatment (83), and patients can be provided with the option to choose not to receive all information about mild or transient side effects (84). Future research should determine the optimal methods of providing information to patients in clinical practice, particularly related to itch.

Second, as demonstrated in Chapter 5, nocebo effects (and possibly placebo effects) on itch can generalize to other stimuli. Clinicians should be aware, that also in clinical practice, undesired nocebo effects on itch regarding an itch treatment can possibly generalize through negative carry-over effects to subsequent itch treatments (85, 86) or to subsequent symptoms.

Third, the study described in Chapter 4 suggests that established nocebo effects on itch can be reversed. We showed that nocebo effects on itch can be reversed by counterconditioning with verbal suggestion. This might be a promising strategy to reverse nocebo effects in clinical practice. For example, before starting a treatment, patients'

expectations, previous treatment experiences, or fear of side effects could be assessed during a screening session to identify patients that are high of risk for nocebo effects (79). Moreover, people who do not respond well to the treatment, possibly partly due to nocebo effects, could be selected. Potential inadequate negative associations about the treatment can subsequently be weakened by a 'booster session'. This implies that there is extra attention to provide realistic information about the beneficial treatment effects. Moreover, stimuli that were previously associated with negative outcomes (e.g., treatment setting, properties of medication or physician) are first associated with positive outcomes, by a counter conditioning procedure (Chapter 4), before starting or continuing the treatment. Future research should focus on translating these results to itch symptoms.

Conclusions

The following main conclusions can be drawn from the findings of the studies presented in this thesis.

Placebo and nocebo effects can be experimentally induced on itch. Most notably, the current findings show that particularly the combination of conditioning and verbal suggestion is effective for inducing placebo and nocebo effects on itch.

Previously established nocebo effects on itch can be effectively reduced using counterconditioning with verbal suggestion. By this strategy, nocebo effects on itch can even be completely reversed resulting in placebo effects.

Reduced nocebo effects on itch can generalize to different itch stimuli, but no evidence was found for generalization of either nocebo effects or reduced nocebo effects on itch to scratching behavior.

Individual characteristics like personality traits or cognitive schemas of itch related memories and expectations can possibly partly explain interindividual differences in placebo and nocebo itch responding.

Together, the current thesis provides further evidence for the role of expectancy learning in placebo and nocebo effects on itch. Knowledge on the formation, reversion, and prediction of placebo and nocebo effects on itch may, in the long term, help improve

therapeutic interventions by enhancing placebo effects and reducing nocebo effects in patients suffering from chronic itch.

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