Placebo and nocebo effects on itch: An experimental approach

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CHAPTER 1

GENERAL INTRODUCTION

Itch is a common symptom of many conditions and diseases (1), and the most common somatosensory symptom in dermatological conditions such as psoriasis and atopic dermatitis (2). It is estimated that almost one in every four people worldwide suffer from chronic itch (> 6 weeks) at some point in their life (2-8). Chronic itch can be a considerable burden for patients and is associated with an impaired quality of life, a reduction in social activities, lowered sleep quality, concentration problems, and depression (2, 9, 10). Unfortunately, treatments have variable and often suboptimal effectiveness (11, 12). Scratching may have an important role in the maintenance and exacerbation of skin conditions due to a vicious itch-scratch circle (12, 13). Over the past years, studies have highlighted that psychological factors, like cognitions, emotions, and behavior, can modulate itch and affect treatment outcomes (13, 14). A factor considerably influencing the experience of itch is treatment expectancies, which can result in placebo and nocebo effects (14-17). So far, little research has been conducted on the role of placebo and nocebo effects on itch.

Placebo and nocebo effects

Placebo effects are positive treatment effects, unrelated to the treatment mechanism, which are induced by patients' expectations of improvement (18, 19). Nocebo effects, the placebo effects' counterpart, are negative treatment effects, induced by patients' expectations of worsening (20). It is known that placebo and nocebo effects play a role in the outcome of treatment effects in a wide range of symptoms and conditions like Parkinson's disease, gastrointestinal disorders, fatigue, nausea, pain, and itch. A sham treatment such as a fake pill or an inert cream can relieve symptoms merely due to the patient's expectation that the treatment will be helpful (e.g., placebo effects), and worsen symptoms when negative treatment effects are expected (i.e., nocebo effects) (21). In a similar way, a patient's expectations can enhance or diminish the treatment effects of a real treatment. Both placebo and nocebo effects are most commonly observed on self-reported outcomes like subjective levels of pain or itch. However, also behaviorally effects can be seen. For example, placebo and nocebo effects can influence tolerance to pain or fatigue and thereby improve or worsen physical performance for example in athletes (22). Moreover, extensive neurobiological research in different fields also indicates that placebo and nocebo effects can be characterized

by changes in brain processes as well as by responses from the immune, neuroendocrine or the autonomic nervous system (23, 24).

In comparison to pain, placebo and nocebo effects have only incidentally been studied on itch. A meta-analysis of clinical trials demonstrated that placebo effects can contribute substantially to the treatment of itch in patients with atopic dermatitis, psoriasis, and idiopathic urticaria (25). The patients in the placebo arm of the trials showed a 24%-reduction in itch symptoms after a placebo treatment with a medium to large effect size (25). With regard to nocebo effects, first indications stem from studies on 'contagious itch'. These studies demonstrated that watching other people scratching, viewing itch related pictures (e.g., pictures of rash or lice), or discussing itch can induce the sensation of itch in healthy persons and patients with chronic itch (26, 27). Expectations are supposed to play an important role in contagious itch (28). Behaviorally, from studies on contagious itch, there is evidence that these effects on itch are also visible on scratching behavior. For example, when participants watched videos of people scratching compared to control videos, they not only reported higher overall itch ratings but also scratched more frequently, with largest effects for patients with chronic itch (27). Experimental research also indicated that placebo and nocebo effects could be induced regarding experimentally evoked itch by using for example histamine or electrical stimulation in healthy participants and patients (16, 17, 29). In these studies placebo and nocebo effects were induced by verbal suggestions that elicit expectations for lower (placebo) or higher (nocebo) itch in the participants. However, methods other than verbal suggestions to induce placebo and nocebo effects have hardly been systematically studied in itch.

Learning in placebo and nocebo effects

Placebo and nocebo effects are a consequence of learned responses, of which expectancies are believed to be the core mechanism (30, 31). Expectancies entail cognitions about future events, experiences, and behavior, and can be formed by various types of cues (verbal, conditioned, and social). In experimental placebo and nocebo research, expectations are most often induced by verbal suggestion or conditioning procedures (32).

Verbal suggestion

Verbal suggestion in placebo research can be described as verbal instructions and persuasive communication regarding the outcome of a certain placebo or active treatment as a form of instructional learning (32). Verbal suggestion is often provided verbally (e.g., by a doctor during a consult), but can for example also be provided in written form (e.g., possible side effects of medication in patient leaflet). Verbal suggestions regarding placebos have been found to induce effects that can be similar to effects of active treatments (19, 33-36). For example, in one study regarding histamine-evoked itch in healthy individuals, a placebo cream along with the verbal suggestion that it was an 'anti-histamine' cream that would decrease itch, led to a significant reduction in itch in comparison to a control group in which the placebo cream was provided without verbal suggestion (29). Moreover, verbal suggestion can also produce nocebo effects (37), and some studies indicated that verbally providing negative information once, can be as strong as the direct experience of negative outcomes (i.e., conditioning, see next paragraph)(38). One of the first studies on verbal suggestion and nocebo-like effects (i.e., when verbal suggestions are not attributed to a nocebo stimulus like a sugar pill) on itch found that patients with atopic dermatitis (AD) reported more itch and had a stronger skin response to a topical histamine application when exaggerated verbal suggestions were given regarding possible skin reaction, than when downplayed suggestions were given (16). These findings are supported by an experimental study in healthy individuals investigating the role of verbal suggestion in nocebo-like effects regarding mechanical-, electrical- and histamine itch stimuli (17). Participants who were told that 95% of the healthy people experience itch from the stimuli to be applied reported significantly higher levels of evoked itch than those who were told that only 5% of the healthy people experience itch from the stimuli. Across different symptoms and conditions, verbal suggestion has provided robust evidence for the formation of placebo as well as nocebo effects (35, 38, 39), and also for itch several studies have confirmed the role of verbal suggestion in placebo and nocebo effects (16, 17, 29, 40).

Conditioning

Conditioning in the context of placebo research is an associative learning procedure in which the experience of a treatment outcome plays a central role. This has mainly been investigated with regard to pain (33, 41, 42). After repeated associations between a conditioned stimulus (CS), which can be represented by several contextual cues (e.g., color

and shape of a pill), and an unconditioned stimulus (US) (e.g., the active agent inside the pill), the CS alone (e.g., placebo pill) can induce a conditioned response (CR) that is similar to that induced by the active drug, i.e., symptom reduction (33, 42-45). An example in clinical practice is when a patient experiences itch relief directly after taking regularly used medication, before the effects of the active ingredients can take place. In an experimental study in patients with atopic dermatitis, conditioning of expectations of pain decrease was achieved by repeatedly surreptitiously reducing the intensity of a painful stimulation when a placebo ointment was applied (46). Results showed that patients as well as healthy individuals experienced less pain after the conditioning procedure along with the verbal suggestion that the ointment was pain reducing. Moreover, results were more robust than when only verbal instructions were provided without the conditioning procedure (46). Placebo research generally shows that whereas verbal suggestion can induce short-term placebo and nocebo effects, conditioning seems particularly relevant to elicit longer term placebo and nocebo effects (31, 47). With regard to itch, only few studies investigated the effects of conditioning (with verbal suggestion)(48, 49). Napadow and colleagues showed that patients with AD experienced more itch from a saline skin prick test when they expected a real allergen, due to previous exposure to the real allergen, than when they were told it was saline (48). Van de Sand and colleagues (49) conditioned nocebo effects in healthy participants regarding thermal modulation of histamine-evoked itch and used a TENS device as placebo. When testing for effects, participants experienced increased itch when they were told the TENS device was active as compared when they were told it was not active, although the intensity of the stimulation was identical (49). In these studies on itch, and also in most studies in other fields like pain, conditioning is combined with verbal suggestion. Because of this entanglement, comparative effects of verbal suggestion versus conditioning are largely unclear. Research investigating the comparative and additive effects of the learning procedures verbal suggestion and conditioning is warranted.

Counteracting nocebo effects

Whereas several studies focused on how to maximize placebo responses, there have been surprisingly few attempts to develop interventions to minimize or reverse nocebo effects. Nocebo effects are not only inherently unpleasant to the individuals who experience them but can also cause substantial social and economic burden (50). Some studies have tried to identify factors contributing to nocebo effects such as patients' personality characteristics

or physicians' communication style, and made some first recommendations how formation of nocebo effects could be minimized (20, 51, 52). However, the induction of nocebo effects cannot always be prevented. Therefore, it is essential to develop strategies to reverse or counteract the substantial harm caused by nocebo effects once they are established.

So far, two studies investigated whether established nocebo effects (33), or nocebo-like effects (53), can be reduced using verbal suggestion procedures. Benedetti and colleagues (54) showed that previously conditioned nocebo effects on induced ischemic arm pain in healthy individuals were completely counteracted by positive verbal suggestions. In the same study, positive verbal suggestions also counteracted the nocebo effects on motor performance of the previous conditioning in patients with Parkinson disease (33). A study from Crichton and colleagues investigated symptom reporting (physical and psychological e.g., headache or worrying) due to windfarm sound. Participants were exposed twice to the same windfarm sound, first after watching a DVD containing negative information about the windfarm sound and the second time after watching a DVD containing positive information. Results showed that whereas during the first exposure to windfarm sound nocebo-like effects were induced, during the second exposure the nocebo-like effects were returned to baseline or even decreased from baseline, indicating placebo-like effects (53). The results of these studies imply that it might be possible to reduce or reverse previously established nocebo effects by positive verbal suggestions.

Extinction is another learning strategy investigated to reverse conditioned nocebo effects (55, 56). Extinction implies the unlearning of a relationship between the conditioned stimulus (e.g., color and shape of a pill) and conditioned response (e.g., increase in itch) after the cues are repetitively presented without the unconditioned stimulus (US) (e.g., the active agent inside the pill). Whereas placebo effects on pain have shown to extinguish due to extinction (57-59), nocebo effects on pain seem more resistant to extinction (38, 55, 60). Other strategies might possibly be more effective in reducing established nocebo effects. Given that learning through conditioning is one of the mechanisms playing a critical role in establishing nocebo effects, counteracting by conditioning, i.e., counterconditioning, might provide a powerful strategy to reduce nocebo effects. Counterconditioning has so far mainly been investigated with regard to fear and evaluative conditioning paradigms (61-63). Results show that counterconditioning can effectively change previously conditioned effects (61-63).

Since extinction seems not sufficient to reduce conditioned nocebo effects, counterconditioning in combination with verbal suggestions might be a promising method to reduce nocebo effects.

Generalization of placebo and nocebo effects

Generalization describes the transfer of formerly gained information to novel stimuli and situations, often as a result of similarity between the original and novel situation (64, 65). Generalization of conditioned responses has been well established in fear conditioning research (66, 67). An initially neutral stimulus (CS) is repeatedly paired with an aversive stimulus such as an electric shock. Generalization occurs when after a few CS-US pairings, not only the CS alone, but also a novel stimulus related to the CS, elicits a fear response. To illustrate, a person might experience fear of all kinds of dogs after one negative experience with one specific aggressive dog. Also in placebo research, initial studies have shown that placebo and nocebo effects can generalize to related stimuli or modalities. Analgesic and hyperalgesic effects on pain perception have shown to generalize to novel stimuli perceptually or conceptually related to the CS (64, 68). Moreover, generalization of placebo and nocebo effects to different modalities can occur. It has been shown that placebo effects induced on pain can generalize to fatigue (69) or to emotion (70-74). To illustrate, in the experimental study from Carlino and colleagues (69) pain was induced using painful stimulation on the fingers and pain tolerance was manipulated using a conditioning procedure on pain intensity and providing verbal suggestion that pain tolerance would increase and fatigue would decrease by the activation of sham electrodes (placebo). Next, participants were subjected to a motor endurance task using a finger flexor device that measured the ability to continue a physical task despite fatigue. Results showed that when applying the previously used placebo electrodes during this motor task, participants reported a reduction in fatigue and showed an increase in the number of flexions (69). Similarly, also with regard to itch, generalization of placebo and nocebo effects might occur, for example with regard to different itch stimuli or scratching behavior. However, this has not yet been investigated.

Individual differences

The magnitude of placebo and nocebo responses has been shown to highly vary among individuals (35, 47, 75). This suggests that differences in individual characteristics may affect

placebo and nocebo responding (76). Many studies have attempted to identify these individual characteristics, mostly focusing on multifaceted expectancy constructs, i.e., personality characteristics that are related to expectations like optimism (characterized by expecting generally positive outcomes) or neuroticism (characterized by expecting generally negative outcomes) (77). Studies have for example found that more optimistic people show greater placebo responses than less optimistic people (78-80), and neuroticism has been shown to be negatively related with placebo effects (30, 81). However these results could not always be replicated (82, 83). Next to personality characteristics, also affective and cognitive factors have been proposed to contribute to placebo and nocebo responding, like state anxiety, stress, memories about the past, and expectations about the future (cognitive schemas) (47, 80, 84). At this moment, no conclusive set of predicting individual characteristics has been identified.

With regard to placebo and nocebo effects on itch, research on the role of individual characteristics is very limited. A study by Scholz and Hermans (16) on nocebo-like effects on itch showed that responders had significant higher trait anxiety scores, greater subjective feelings of illness, more illness-related social problems, and catastrophized more about the disease consequences. Another study on placebo and nocebo-like effects assessed the role of personality characteristics neuroticism, social desirability, imaginative involvement, and suggestibility, but found no significant correlations with placebo or nocebo effects on itch (17). Furthermore, also research into contagious itch has explored the possible predicting role of individual characteristics (27). In patients with chronic skin diseases, the degree of contagious itch and scratching have found to be associated with agreeableness, self-consciousness, and depression (85, 86). In healthy individuals, neuroticism and state anxiety were linked to the extent of induced contagious itch (87, 88). Again, these findings in patients as well as healthy individuals could not always be replicated (85, 86, 89). Considering the limited amount of research (i.e., mainly on contagious itch) and inconsistent findings, it is unclear what individual characteristics may predict placebo and nocebo effects on itch.

Aim and outline thesis

This thesis aims to increase understanding of experimentally induced placebo and nocebo effects on itch. Specifically, the individual and combined effectiveness of the

expectation inductions of verbal suggestion and conditioning, the possibility to reverse nocebo effects, the generalizability of nocebo effects on itch to scratching and another somatosensory itch stimulus, and the role of individual characteristics in placebo and nocebo effects on itch were investigated.

Chapter 2 includes a brief review of what is known about placebo and nocebo effects on itch. We discuss the link between placebo and nocebo effects on itch and previous studies on contagious itch. Furthermore, predictors of contagious itch and placebo and nocebo effects on itch are discussed.

Chapter 3 presents the results of an experiment studying the individual and combined effects of different expectation inductions on placebo and nocebo effects on itch. Specifically, we assess the effects of verbal suggestion, conditioning, and the combination of verbal suggestion and conditioning on electrically induced itch in healthy individuals. Additionally, the involvement of several individual characteristics is explored.

Chapter 4 describes an experiment studying the reversibility of nocebo effects on itch. Hereby we assess whether nocebo effects induced by conditioning and verbal suggestion can be reversed using a positive expectation induction combining conditioning and verbal suggestion. We also investigate the possible generalization of nocebo effects with regard to electrically induced itch to a different itch stimulus, i.e., histamine iontophoresis. Furthermore, the role of individual characteristics in placebo and nocebo effects is explored.

Chapter 5 reports on an experiment in which the generalizability of nocebo effects from itch to scratching behavior is studied. Specifically, we investigate whether nocebo effects and reversed nocebo effects on electrically induced itch (see Chapter 4) generalize to scratching behavior. Additionally, generalization of effects on scratching behavior evoked by the itch stimulus histamine is explored.

Chapter 6 presents the results of a study on interindividual differences in placebo and nocebo responding on itch. Within an experimental study on placebo and nocebo effects on itch, we investigate the role of individual cognitive schemas of itch related memories and expectations in placebo and nocebo responding on itch. Specifically, we assess the role of specificity and valence of autobiographical memories and expectations that are related to itch in placebo and nocebo responding on itch.

Chapter 7 provides a general summary and integrative discussion of the results described in the different studies. Moreover, limitations, clinical implications and future directions are presented.

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