Placebo and nocebo effects on itch: An experimental approach

Bartels, D.J.P.

DANIELLE BARTELS

PLACEBO - AND - NOCEBO EFFECTS - ON - ITCH

AN EXPERIMENTAL APPROACH

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Danielle J.P. Bartels

Author: Danielle Bartels
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Prof. dr. A.J.W. van der Does (secretaris)

Prof. dr. E.M.G.J de Jong (Radboud University Medical Center)

Prof. dr. H.C. Dijkerman (Utrecht University)

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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.

References

1. Yosipovitch G, Samuel LS. Neuropathic and psychogenic itch. Dermatologic therapy. 2008;21(1):32-41.
2. Stander S, Schafer I, Phan NQ, Blome C, Herberger K, Heigel H, et al. Prevalence of chronic pruritus in Germany: results of a cross-sectional study in a sample working population of 11,730. Dermatology. 2010;221(3):229-35.
3. Mollanazar NK, Koch SD, Yosipovitch G. Epidemiology of Chronic Pruritus: Where Have We Been and Where Are We Going? Curr Dermatol Rep. 2015;4(1):20-9.
4. Weisshaar E, Dalgard F. Epidemiology of itch: adding to the burden of skin morbidity. Acta Derm Venereol. 2009;89(4):339-50.
5. Matterne U, Apfelbacher CJ, Vogelgsang L, Loerbroks A, Weisshaar E. Incidence and determinants of chronic pruritus: a population-based cohort study. Acta Derm Venereol. 2013;93(5):532-7.
6. Matterne U, Apfelbacher CJ, Loerbroks A, Schwarzer T, Buttner M, Ofenloch R, et al. Prevalence, correlates and characteristics of chronic pruritus: a population-based cross-sectional study. Acta Derm Venereol. 2011;91(6):674-9.
7. Matterne U, Strassner T, Apfelbacher CJ, Diepgen TL, Weisshaar E. Measuring the prevalence of chronic itch in the general population: development and validation of a questionnaire for use in large-scale studies. Acta Derm Venereol. 2009;89(3):250-6.
8. Dalgard F, Lien L, Dalen I. Itch in the community: associations with psychosocial factors among adults. J Eur Acad Dermatol Venereol. 2007;21(9):1215-9.
9. Schneider G, Driesch G, Heuft G, Evers S, Luger TA, Stander S. Psychosomatic cofactors and psychiatric comorbidity in patients with chronic itch. Clin Exp Dermatol. 2006;31(6):762-7.
10. Zachariae R, Zachariae CO, Lei U, Pedersen AF. Affective and sensory dimensions of pruritus severity: associations with psychological symptoms and quality of life in psoriasis patients. Acta Derm Venereol. 2008;88(2):121-7.
11. Grundmann S, Stander S. Chronic pruritus: clinics and treatment. Ann Dermatol. 2011;23(1):1-11.
12. Yosipovitch G, Papoiu AD. What causes itch in atopic dermatitis? Current allergy and asthma reports. 2008;8(4):306-11.
13. Verhoeven EW, de Klerk S, Kraaimaat FW, van de Kerkhof PC, de Jong EM, Evers AW. Biopsychosocial mechanisms of chronic itch in patients with skin diseases: a review. Acta Derm Venereol. 2008;88(3):211-8.
14. Evers AWM, Peerdeman KJ, van Laarhoven AIM. What is new in the psychology of chronic itch? Exp Dermatol. 2019;28(12):1442-7.
15. Evers AW. Using the placebo effect: how expectations and learned immune function can optimize dermatological treatments. Exp Dermatol. 2017;26(1):18-21.
16. Scholz O, Hermanns N. Illness behavior and cognitions influence the perception of itching of patients suffering from atopic dermatitis. Z Klin Psychol. 1994;23:127-35.
17. van Laarhoven AI, Vogelaar ML, Wilder-Smith OH, van Riel PL, van de Kerkhof PC, Kraaimaat FW, et al. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain. 2011;152(7):1486-94.
18. Benedetti F. Mechanisms of placebo and placebo-related effects across diseases. Annu Rev Pharmacol. 2008;48:33-60.
19. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: Recent advances and current thought. Annu Rev Psychol. 2008;59:565-90.
20. Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. Psychosom Med. 2011;73(7):598-603.
21. Benedetti F, Carlino E, Pollo A. How Placebos Change the Patient's Brain. Neuropsychopharmacol. 2011;36(1):339-54.
22. Fiorio M. Modulation of the Motor System by Placebo and Nocebo Effects. Int Rev Neurobiol. 2018;139:297-319.

23. Atlas LY, Wager TD. A meta-analysis of brain mechanisms of placebo analgesia: consistent findings and unanswered questions. Handbook of experimental pharmacology. 2014;225:37-69.
24. Schedlowski M, Enck P, Rief W, Bingel U. Neuro-Bio-Behavioral Mechanisms of Placebo and Nocebo Responses: Implications for Clinical Trials and Clinical Practice. Pharmacol Rev. 2015;67(3):697-730.
25. van Laarhoven AI, van der Sman-Mauriks IM, Donders AR, Pronk MC, van de Kerkhof PC, Evers AW. Placebo Effects on Itch: A Meta-Analysis of Clinical Trials of Patients with Dermatological Conditions. J Invest Dermatol. 2015;135(5):1234-43.
26. Papoiu AD, Wang H, Coghill RC, Chan YH, Yosipovitch G. Contagious itch in humans: a study of visual 'transmission' of itch in atopic dermatitis and healthy subjects. Br J Dermatol. 2011;164(6):1299-303.
27. Schut C, Grossman S, Gieler U, Kupfer J, Yosipovitch G. Contagious itch: what we know and what we would like to know. Frontiers in human neuroscience. 2015;9:57.
28. van Laarhoven AIM, Holle H. Optimizing audiovisual itch induction: the role of attention and expectancy. Br J Dermatol. 2019.
29. Darragh M, Chang JW, Booth RJ, Consedine NS. The placebo effect in inflammatory skin reactions: The influence of verbal suggestion on itch and weal size. Journal of psychosomatic research. 2015;78(5):489-94.
30. Horing B, Weimer K, Muth ER, Enck P. Prediction of placebo responses: a systematic review of the literature. Front Psychol. 2014;5:1079.
31. Benedetti F. Placebo effects: Oxford University Press, USA; 2014.
32. Colloca L, Miller FG. How placebo responses are formed: a learning perspective. Philos Trans R Soc Lond B Biol Sci. 2011;366(1572):1859-69.
33. Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. J Neurosci. 2003;23(10):4315-23.
34. Wampold BE, Minami T, Tierney SC, Baskin TW, Bhati KS. The placebo is powerful: estimating placebo effects in medicine and psychotherapy from randomized clinical trials. J Clin Psychol. 2005;61(7):835-54.
35. Petersen GL, Finnerup NB, Colloca L, Amanzio M, Price DD, Jensen TS, et al. The magnitude of nocebo effects in pain: a meta-analysis. Pain. 2014;155(8):1426-34.
36. Peerdeman KJ, van Laarhoven AI, Keij SM, Vase L, Rovers MM, Peters ML, et al. Relieving patients' pain with expectation interventions: a meta-analysis. Pain. 2016;157(6):1179-91.
37. Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: Unraveling the mechanisms of the nocebo effect. Neuroscience. 2007;147(2):260-71.
38. Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. Pain. 2008;136(1-2):211-8.
39. Vase L, Riley JL, 3rd, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. Pain. 2002;99(3):443-52.
40. Schut C, Radel A, Frey L, Gieler U, Kupfer J. Role of personality and expectations for itch and scratching induced by audiovisual itch stimuli. European journal of pain. 2016;20(1):14-8.
41. Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F. How the number of learning trials affects placebo and nocebo responses. Pain. 2010;151(2):430-9.
42. Jensen K, Kirsch I, Odmalm S, Kaptchuk TJ, Ingvar M. Classical conditioning of analgesic and hyperalgesic pain responses without conscious awareness. P Natl Acad Sci USA. 2015;112(25):7863-7.
43. Ader R. Processes underlying placebo effects - The preeminence of conditioning. Pain Forum. 1997;6(1):56-8.
44. Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. J Neurosci. 1999;19(1):484-94.
45. Stewart-Williams S, Podd J. The placebo effect: dissolving the expectancy versus conditioning debate. Psychological bulletin. 2004;130(2):324-40.
46. Klinger R, Soost S, Flor H, Worm M. Classical conditioning and expectancy in placebo hypoalgesia: a randomized controlled study in patients with atopic dermatitis and persons with healthy skin. Pain. 2007;128(1-2):31-9.

47. Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: Psychological and neurobiological mechanisms. Pain. 2013;154(4):511-4.
48. Napadow V, Li A, Loggia ML, Kim J, Mawla I, Desbordes G, et al. The imagined itch: brain circuitry supporting nocebo-induced itch in atopic dermatitis patients. Allergy. 2015;70(11):1485-92.
49. van de Sand MF, Menz MM, Sprenger C, Buchel C. Nocebo-induced modulation of cerebral itch processing - An fMRI study. Neuroimage. 2018;166:209-18.
50. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. JAMA. 2002;287(5):622-7.
51. Colloca L, Finniss D. Nocebo effects, patient-clinician communication, and therapeutic outcomes. JAMA. 2012;307(6):567-8.
52. Evers AWM, Colloca L, Blease C, Annoni M, Atlas LY, Benedetti F, et al. Implications of Placebo and Nocebo Effects for Clinical Practice: Expert Consensus. Psychotherapy and psychosomatics. 2018;87(4):204-10.
53. Crichton F, Petrie KJ. Accentuate the positive: Counteracting psychogenic responses to media health messages in the age of the Internet. Journal of psychosomatic research. 2015;79(3):185-9.
54. Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. J Neurosci. 2003;23(10):4315-23.
55. Colagiuri B, Quinn VF, Colloca L. Nocebo hyperalgesia, partial reinforcement, and extinction. J Pain. 2015.
56. Colagiuri B, Quinn VF. Autonomic Arousal as a Mechanism of the Persistence of Nocebo Hyperalgesia. J Pain. 2018;19(5):476-86.
57. Colloca L, Benedetti F. Duration over time of learned placebo analgesic responses. Eur Neuropsychopharm. 2010;20:S35-S.
58. Colloca L, Benedetti F. How prior experience shapes placebo analgesia. Pain. 2006;124(1-2):126-33.
59. Au Yeung ST, Colagiuri B, Lovibond PF, Colloca L. Partial reinforcement, extinction, and placebo analgesia. Pain. 2014;155(6):1110-7.
60. Voudouris NJ, Peck CL, Coleman G. The role of conditioning and verbal expectancy in the placebo response. Pain. 1990;43(1):121-8.
61. Kerkhof I, Vansteenwegen D, Baeyens F, Hermans D. Counterconditioning. Experimental psychology. 2015.
62. Van Gucht D, Baeyens F, Vansteenwegen D, Hermans D, Beckers T. Counterconditioning reduces cue-induced craving and actual cue-elicited consumption. Emotion. 2010;10(5):688-95.
63. Raes AK, De Raedt R. The effect of counterconditioning on evaluative responses and harm expectancy in a fear conditioning paradigm. Behav Ther. 2012;43(4):757-67.
64. Koban L, Kusko D, Wager TD. Generalization of learned pain modulation depends on explicit learning. Acta Psychol (Amst). 2018;184:75-84.
65. Shepard RN. Toward a universal law of generalization for psychological science. Science. 1987;237(4820):1317-23.
66. Dunsmoor JE, Mitroff SR, LaBar KS. Generalization of conditioned fear along a dimension of increasing fear intensity. Learn Mem. 2009;16(7):460-9.
67. Dymond S, Dunsmoor JE, Vervliet B, Roche B, Hermans D. Fear Generalization in Humans: Systematic Review and Implications for Anxiety Disorder Research. Behav Ther. 2015;46(5):561-82.
68. Liu C, Chen L, Yu R. Category-based generalization of placebo and nocebo effects. Acta Psychol (Amst). 2019;199:102894.
69. Carlino E, Guerra G, Piedimonte A. Placebo effects: From pain to motor performance. Neurosci Lett. 2016;632:224-30.
70. Zhao Y, Zhang J, Yuan L, Luo J, Guo J, Zhang W. A transferable anxiolytic placebo effect from noise to negative effect. J Ment Health. 2015;24(4):230-5.
71. Zhang W, Qin S, Guo J, Luo J. A follow-up fMRI study of a transferable placebo anxiolytic effect. Psychophysiology. 2011;48(8):1119-28.
72. Zhang W, Luo J. Neural bases of reappraisal regulatory effect on negative emotion in high reappraisers. Neural Regen Res. 2012;7(32):2542-7.

73. Zhang W, Luo J. The transferable placebo effect from pain to emotion: changes in behavior and EEG activity. Psychophysiology. 2009;46(3):626-34.
74. Zhang W, Guo J, Zhang J, Luo J. Neural mechanism of placebo effects and cognitive reappraisal in emotion regulation. Prog Neuropsychopharmacol Biol Psychiatry. 2013;40:364-73.
75. Colagiuri B, Schenk LA, Kessler MD, Dorsey SG, Colloca L. The placebo effect: From concepts to genes. Neuroscience. 2015;307:171-90.
76. Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of context effects on health outcomes: a systematic review. Lancet. 2001;357(9258):757-62.
77. Peerdeman KJ, van Laarhoven AI, Peters ML, Evers AW. An Integrative Review of the Influence of Expectancies on Pain. Front Psychol. 2016;7:1270.
78. Geers AL, Kosbab K, Helfer SG, Weiland PE, Wellman JA. Further evidence for individual differences in placebo responding: an interactionist perspective. Journal of psychosomatic research. 2007;62(5):563-70.
79. Geers AL, Wellman JA, Fowler SL, Helfer SG, France CR. Dispositional optimism predicts placebo analgesia. J Pain. 2010;11(11):1165-71.
80. Morton DL, Watson A, El-Deredy W, Jones AK. Reproducibility of placebo analgesia: Effect of dispositional optimism. Pain. 2009;146(1-2):194-8.
81. Pecina M, Azhar H, Love TM, Lu T, Fredrickson BL, Stohler CS, et al. Personality trait predictors of placebo analgesia and neurobiological correlates. Neuropsychopharmacol. 2013;38(4):639-46.
82. Horing B, Weimer K, Schrade D, Muth ER, Scisco JL, Enck P, et al. Reduction of motion sickness with an enhanced placebo instruction: an experimental study with healthy participants. Psychosom Med. 2013;75(5):497-504.
83. Jaksic N, Aukst-Margetic B, Jakovljevic M. Does personality play a relevant role in the placebo effect? Psychiatr Danub. 2013;25(1):17-23.
84. Flaten MA, Aslaksen PM, Finset A, Simonsen T, Johansen O. Cognitive and emotional factors in placebo analgesia. Journal of psychosomatic research. 2006;61(1):81-9.
85. Schut C, Muhl S, Reinisch K, Classen A, Jager R, Gieler U, et al. Agreeableness and Self-Consciousness as Predictors of Induced Scratching and Itch in Patients with Psoriasis. International journal of behavioral medicine. 2015.
86. Schut C, Bosbach S, Gieler U, Kupfer J. Personality traits, depression and itch in patients with atopic dermatitis in an experimental setting: a regression analysis. Acta Derm Venereol. 2014;94(1):20-5.
87. Holle H, Warne K, Seth AK, Critchley HD, Ward J. Neural basis of contagious itch and why some people are more prone to it. Proc Natl Acad Sci U S A. 2012;109(48):19816-21.
88. Ogden J, Zoukas S. Generating physical symptoms from visual cues: An experimental study. Psychology, health & medicine. 2009;14(6):695-704.
89. Schut C, Reinisch K, Classen A, Andres S, Gieler U, Kupfer J. Agreeableness as Predictor of Induced Scratching in Patients with Atopic Dermatitis: A Replication Study. Acta Derm Venereol. 2018;98(1):32-7.

CHAPTER 2

PLACEBO AND NOCEBO EFFECTS ON ITCH: EFFECTS, MECHANISMS, AND PREDICTORS

MINI REVIEW

Published as

Bartels, D.J.P, van Laarhoven, A. I.M, van de Kerkhof, P.C.M, & Evers, A.W.M (2016). Placebo and nocebo effects on itch: effects, mechanisms, and predictors. *European journal of pain, 20(1),* 8-13.

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Abstract

Placebo and nocebo effects have been extensively studied in the field of pain and more recently also on itch. In accordance with placebo research on pain, expectancy learning via verbal suggestion or conditioning has shown to induce placebo and nocebo effects on itch, in which the combination of both procedures seems most promising. Moreover, itch can also be transferred 'contagiously' in which suggestion and social behavioural learning seem to play a role. With regard to predictors of placebo and nocebo responding on itch and contagious itch, preliminary evidence suggests a role for individual psychological characteristics and personality traits regarding negative outcome expectancies. Although findings on placebo and nocebo effects on itch seem comparable to pain, we have only just begun to understand the underlying mechanisms and predictors of placebo and nocebo effects on itch

Introduction

Placebo and nocebo effects are known to play a key role in treatment effects of various symptoms and conditions, and have extensively been studied, particularly in the field of pain. Similar to pain, itch is a somatosensory sensation that can be a considerable burden for patients, especially when symptoms are chronic. Evidence for the role of placebo and nocebo effects on itch has increased over the last decade. The suggestibility of itch is underlined by literature on 'contagious itch': watching other people scratching or discussing itch can induce the sensation of itch and an urge to scratch (e.g. Papoiu et al., 2011; Schut et al., 2015a). More direct evidence has been provided by a recent meta-analysis of clinical trials showing that placebo effects can contribute substantially to the treatment of itch in patients with dermatological conditions (van Laarhoven et al., 2015). In addition, various experimental studies have shown that placebo and nocebo effects can influence the experience of itch (e.g. Scholz and Hermanns, 1994; van Laarhoven et al., 2011; Bartels et al., 2014; Darragh et al., 2015).

With regard to the underlying psychological and neurobiological mechanisms, there is a large body of evidence underscoring the importance of expectancy learning in eliciting placebo and nocebo responses (Colloca and Miller, 2011; Colloca et al., 2013). In view of the considerable interindividual variance in placebo and nocebo responding, a main question to be answered is whether placebo and nocebo responses can be predicted. In other words: who is a placebo/nocebo responder and who is not? Although this question has been under investigation, predominantly in the field of pain, the concerning literature is still scarce and incongruent (Colloca et al., 2013).

This review aims to provide a state of the art overview of recent and current placebo and nocebo research on itch in comparison with previous findings on pain, with a special emphasis on the underlying mechanisms of expectancy learning and possible predictors.

Effects and mechanisms in placebo and nocebo effects on itch

Placebo research across different symptoms and conditions has identified verbal suggestion, social learning, and conditioning as main mechanisms in the induction of placebo and nocebo effects (Enck et al., 2008; Colloca and Miller, 2011; Colloca et al., 2013).

Particularly social behavioural learning and suggestion seem also to play a role in contagiously transferred itch. Social learning implies learning by observing others, whereby the behaviour of the demonstrator modifies the subsequent behaviour of the observer (Colloca and Miller, 2011). For example, it has been shown that a lecture about itch along with presenting pictures of insects, scratch marks, and allergic reactions, increases itching and accompanying scratching behaviour in an audience, as compared to a neutral lecture (Niemeier and Gieler, 2000). The phenomenon of contagious itch has also systematically been examined in both patients and healthy subjects. In one study, patients with atopic dermatitis (AD) and healthy subjects watched a video either with people scratching or with neutral content, while a histamine or a placebo stimulus was administered. The patients who watched the video with people scratching reported significantly more itch and scratched more frequently than the patients who watched the neutral video, not only when receiving histamine but also during the placebo stimulus. This increase in self-reported itch and scratching behaviour was not observed in the healthy subjects in this study (Papoiu et al., 2011). However, several other studies on contagious itch demonstrated significant increases in itch and scratching in both patients and healthy subjects (Ogden and Zoukas, 2009; Holle et al., 2012; Lloyd et al., 2013; Ward et al., 2013; Schut et al., 2014), with some studies demonstrating more pronounced responses in patients with chronic itch than in healthy subjects (Papoiu et al., 2011; Schut et al., 2014). In addition, Holle et al. (2012) attempted to identify neural brain networks involved in the generation of contagious itch. Functional Magnetic Resonance Imaging data indicated that when subjects watched video clips of someone scratching in comparison to control video clips, neural regions linked to the physical perception of itch, including the anterior insula, premotor cortex, primary somatosensory cortex and prefrontal cortex, were activated.

In line with research on pain, nocebo effects have been investigated in several experimental studies in which expectations regarding itch stimuli were induced by verbal suggestion. Verbal suggestion consists of delivering instructions for benefit or worsening so that the subject expects improvement or worsening of symptoms, respectively (Colloca and Miller, 2011; Colloca et al., 2013). One of the first studies on verbal suggestion and itch found that patients with AD reported more itch and had a stronger skin response to a topical histamine application when exaggerated verbal suggestions were given, than when downplayed suggestions were given (Scholz and Hermanns, 1994). These findings are

supported by a study in healthy subjects investigating the role of verbal suggestion in nocebo effects regarding mechanical-, electrical- and histamine itch stimuli (van Laarhoven et al., 2011). 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. Further evidence for the role of verbal suggestion in nocebo effects on itch comes from a study investigating the neurobiology of nocebo effects in patients with AD (Napadow et al., 2013). This study showed that patients experienced more itch from a saline skin prick test when they expected a real allergen than when they were told it was saline. Their functional Magnetic Resonance Imaging data showed that when applying saline while patients expected a real allergen, similar brain responses were observed as with the previously applied real allergen, with greater activation in the striatum and the dorsolateral prefrontal cortex. These regions have previously also been linked to placebo- or nocebo-induced brain processes related to pain and its regulation (Enck et al., 2008; Colloca et al., 2013).

Also placebo effects on itch can be induced by verbal suggestion. In a recent investigation in healthy subjects a significant reduction in self-reported itch was found during histamine application when verbal suggestions for reduced itch and wheal size where given in comparison to a control procedure (Darragh et al., 2015). With regard to wheal size no significant decrease due to the verbal suggestion was demonstrated. The latter finding is consistent with a prior study of the same research group, in which no significant placebo effect on skin reaction was found after a verbal suggestion procedure concerning reduced wheal size in comparison to a control procedure (Darragh et al., 2013). Such findings are in line with research on pain, showing that verbal suggestions alone are insufficient to induce physiological indications of a placebo or nocebo response.

Whereas placebo research has generally shown that verbal suggestion can induce short-term placebo and nocebo effects on self-reported pain, conditioning seems particularly relevant to induce longer term placebo and nocebo effects on pain and physiological responses (Colloca et al., 2013). A conditioning procedure comprises of simulating benefit or worsening by pairing a neutral stimulus (e.g. shape, colour and size of a placebo pill) with an unconditioned stimulus (e.g. the pharmacological effect of a drug or a stimulus that is surreptitiously lowered or increased, respectively), which leads to a learned association

(Colloca et al., 2013). In an experimental study Bartels et al. (2014) examined the role of conditioning in inducing placebo and nocebo effects on itch in healthy subjects. Expectations regarding electrical itch stimuli were induced by verbal suggestion, conditioning or a combination of both procedures, and compared with a control group without expectation induction. The conditioning procedure consisted of the pairing of visual cues with surreptitiously lowered or increased itch stimuli. Particularly, the combination of conditioning and verbal suggestion was demonstrated to be effective in inducing placebo and nocebo effects on itch. Data from a study in patients with AD also emphasize the added value of conditioning in placebo effects on itch (Sölle et al., 2014). More specifically, itch was induced experimentally and patients were randomly assigned to one of three groups: (1) antihistamine + conditioning and verbal suggestion; (2) antihistamine and verbal suggestion; (3) saline + conditioning and verbal suggestion. The conditioning procedure consisted of the pairing of antihistamine or saline with decreased itch sensations. Results showed that all three patient groups reported less itch compared to baseline measurement. More importantly, the group receiving antihistamine with a verbal suggestion and conditioning procedure reported significantly less itch compared to the antihistamine group with solely verbal suggestions.

Conditioning procedures have also shown to affect physiological placebo responses related to itch. In a study in patients with allergic rhinitis, Goebel et al. (2008) carried out a pharmacological conditioning procedure in which an H_1-receptor antagonist was paired with a novel-tasting drink on five consecutive days, after which, in the evocation phase, the H_1-receptor antagonist was replaced by a placebo. In the evocation phase, patients reported less subjective symptoms (combined score that included itch) and showed a reduced skin response to the skin prick test when administering the drink along with a placebo pill (Goebel et al., 2008). A study in patients with house dust mite allergy revealed similar results in subjective symptoms and wheal size after a comparable pharmacological conditioning procedure with desloratadine and a novel-tasting drink (Vits et al., 2013). Interestingly, placebo effects were not only observed in the pharmacologically conditioned group but also in the placebo conditioned group. In both groups, a significant decrease in subjective symptoms and wheal size was found when compared to the natural history group. These preliminary effects on conditioning inflammatory skin reactions in itch are consistent with previous research showing

that conditioning procedures can induce placebo and nocebo effects on physiological processes including immune responses and hormone secretion (Enck et al., 2008).

In summary, there is considerable evidence that both placebo and nocebo effects on itch can be induced by expectancy learning via verbal suggestion and conditioning. Similar to research in pain, verbal suggestion particularly seems to affect subjective measures of self-reported itch, while conditioning might be necessary for inducing physiological responses such as wheal size. The combination of verbal suggestion and conditioning seems most promising for inducing placebo and nocebo effects on itch. Suggestion and social behavioural learning might play a role in contagious itch. However, more research regarding social learning and other possible mechanisms in contagious itch and placebo and nocebo effects is warranted.

Predictors of placebo and nocebo effects on itch

The magnitude of placebo and nocebo responses, for example, regarding pain, has been shown to highly vary among subjects (Petersen et al., 2014). It has been proposed that individual characteristics like personality traits might affect placebo and nocebo responding, but up to now no specific set of predicting characteristics has been identified. With respect to itch, potential individual characteristics predicting placebo and nocebo responding have not systematically been inventoried yet.

With regard to contagious itch and nocebo effects on itch, psychological characteristics and personality traits related to negative outcome expectancies seem to be of importance in predicting effects on itch, although evidence is mixed. Specifically, higher levels of neuroticism and state anxiety have been found to be associated with higher levels of contagious itch in healthy subjects (Ogden and Zoukas, 2009; Holle et al., 2012). In a study in patients with chronic itch, depression, but not neuroticism and anxiety, has been shown to significantly predict experienced contagious itch (Schut et al., 2014). Depressive symptoms and trait anxiety have also been found to be significantly correlated with nocebo responses on itch (Scholz and Hermanns, 1994; Bartels et al., 2014). Although neuroticism was not found to be associated with nocebo responding (van Laarhoven et al., 2011; Bartels et al., 2014), more worrying was associated with a greater nocebo response (Bartels et al., 2014). The tendency to worry about itch, as indicator of negative outcome expectancies, has also shown to worsen clinical itch in a prospective study in patients with psoriasis (PS) (Verhoeven et al., 2009).

Moreover, a study investigating the role of individual characteristics in placebo effects on itch in the placebo arm of a dermatological clinical trial showed that placebo responders, rather than placebo non-responders, were more likely to report that they did not tend to be unusually sensitive to most drugs (Garshick et al., 2014). This finding corresponds to earlier findings in pain demonstrating for example that a negative attitude towards medication can be related to a smaller placebo response (Kamping, 2014). Markedly, until now hardly any significant associations with regard to individual characteristics related to positive outcome expectancies and placebo responses on itch have been found (van Laarhoven et al., 2011; Bartels et al., 2014; Garshick et al., 2014). This is in contrast with studies investigating placebo responses on pain, which found for example evidence that optimists might be better placebo responders (Colloca et al., 2013).

Other individual characteristics investigated in relation to itch placebo responding or contagious itch include agreeableness and public self-consciousness. In contagious itch, lower agreeableness and the combination of lower agreeableness and higher public self-consciousness were found to predict increased scratching behaviour in patients with PS (Schut et al., 2014), and higher public self-consciousness also predicted greater self-reported itch in patients with PS (Schut et al., 2015b). In healthy subjects, however, these individual characteristics did not predict contagious itch or scratching (Schut et al., 2014, 2015b). Similarly, in a dermatological clinical trial no significant difference in public self-consciousness was found between the placebo responders and the placebo non responders (Garshick et al., 2014). In addition, with regard to nocebo effects on itch, higher levels of imagination (Scholz and Hermanns, 1994) and lower levels of extraversion (Bartels et al.,

2014) and have been found to be associated with greater nocebo responses. The role of imaginative involvement or suggestibility, however, was not confirmed by a study on placebo and nocebo effect on itch, nor was there a significant association between social desirability and placebo or nocebo responding (van Laarhoven et al., 2011).

Preliminarily data on the role of individuals' memories and expectations related to itch suggests that cognitive schemas regarding itch might be associated with placebo and nocebo responses on itch. In this study, conducted by our research group, several test previously validated in pain and other conditions, measuring specificity of memories (Autobiographical Memory test) (Williams and Broadbent, 1986), specificity of expectations (Future Event Task)

(Williams et al., 1996), and valence of memories and expectations (Self-referential endorsement and recall task) (Pincus et al., 1995), were modified for itch and applied in healthy subjects before a placebo and nocebo induction protocol. Explorative results revealed some associations between a higher specificity of itch-related memories with a greater nocebo effect, as well as a higher specificity of itch-related expectations with a greater placebo effect. The latter finding with regard to future expectations (but not the finding with regard to memories) is in accordance with theories underlying autobiographical memory and future expectations, showing that people who are more specific in their memories and expectations, experience less depressive symptoms as well as other negative outcomes (Williams et al., 1996, 2007). Explorative results further suggest that valence of memories and expectations do not seem to systematically influence placebo and nocebo responding, but associations were found between more reported expectations regarding itch related words and a smaller nocebo effect. More research into the predicting role of cognitive itch schemas in placebo and nocebo responding is needed. In particular, research in patients with chronic itch is warranted, as they might have altered cognitive schemas as a consequence of long-term suffering from itch.

As far as itch is concerned, no neurobiological studies have been conducted on the prediction of placebo and nocebo responding. Several studies on pain have, however, identified brain patterns in, e.g., emotional appraisal circuits and pain regulation as predictors of individual differences in placebo responses on pain (Wager et al., 2011). Furthermore, no research regarding genetic predictors has been conducted yet with regard to placebo responding on itch, in contrast to some preliminary evidence in pain (Colloca et al., 2013).

Taken together, research on predictors of placebo and nocebo responses on itch is still very preliminary, with some indications for the role of individual characteristics related to negative outcome expectancies and possible promising findings for concepts related to memories and future expectations.

Conclusions

Clinical and experimental research shows that placebo and nocebo effects can play a significant role on itch. Similar to placebo research on pain, expectancy learning via verbal suggestion and conditioning plays a key role in placebo and nocebo effects on itch.

Additionally, exclusively for itch, itch can also be transmitted contagiously, in which social behavioural learning might to play a role. Comparable to pain, suggestion procedures seem sufficient to induce short term nocebo effects and possibly also placebo effects on itch, however, learning by conditioning seems necessary to induce physiological effects. Up to now, the combination of conditioning and verbal suggestion seems most promising for inducing both placebo and nocebo effects on itch and its physiological correlates. In future studies, exploring the combined effect of expectancy learning by suggestion and/or conditioning with contagious itch manipulations in placebo and nocebo effects on itch is recommended. With regard to predicting placebo and nocebo responses on itch, including contagious itch responses, psychological characteristics and personality traits related to negative outcome expectancies seem to be of importance. These finding are similar to research findings in pain. Additionally, also research investigating neurobiological mechanisms underlying placebo and nocebo effects on itch is needed. Particularly in patients with chronic itch symptoms, knowledge on the role of expectancy learning mechanisms and possible predictors in placebo and nocebo effects on itch is warranted. Clinical practice could directly benefit from this knowledge, to improve existing itch treatments for patients with skin conditions suffering from chronic itch.

References

Bartels, D.J., van Laarhoven, A.I., Haverkamp, E.A., Wilder-Smith, O.H., Donders, A.R., van Middendorp, H., van de Kerkhof, P.C., Evers, A.W. (2014). Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. PLoS ONE 9, e91727.

Colloca, L., Miller, F.G. (2011). How placebo responses are formed: A learning perspective. Philos Trans R Soc Lond B Biol Sci 366, 1859–1869.

Colloca, L., Klinger, R., Flor, H., Bingel, U. (2013). Placebo analgesia: Psychological and neurobiological mechanisms. Pain 154, 511–514.

Darragh, M., Booth, R.J., Koschwanez, H.E., Sollers, J. 3rd, Broadbent, E. (2013). Expectation and the placebo effect in inflammatory skin reactions: A randomised-controlled trial. J Psychosom Res 74, 439–443.

Darragh, M., Chang, J.W., Booth, R.J., Consedine, N.S. (2015). The placebo effect in inflammatory skin reactions: The influence of verbal suggestion on itch and weal size. J Psychosom Res 78, 489–494.

Enck, P., Benedetti, F., Schedlowski, M. (2008). New insights into the placebo and nocebo responses. Neuron 59, 195–206.

Garshick, M.K., Chang, A.L., Kimball, A.B. (2014). Only skin deep: Optimism and public self-consciousness did not associate with the placebo response in a dermatology clinical trial. J Drugs Dermatol 13, 719–722.

Goebel, M.U., Meykadeh, N., Kou, W., Schedlowski, M., Hengge, U.R. (2008). Behavioral conditioning of antihistamine effects in patients with allergic rhinitis. Psychother Psychosom 77, 227–234.

Holle, H., Warne, K., Seth, A.K., Critchley, H.D., Ward, J. (2012). Neural basis of contagious itch and why some people are more prone to it. Proc Natl Acad Sci U S A 109, 19816–19821.

Kamping, S., Müller, M., Klinger, R., Schmitz, J., Flor, H. (2014). Analgesics in chronic back pain: The significance of patient attitudes to them and prior experience with them for placebo responses. Zeitschrift für Psychologie 222, 179–185. doi: 10.1027/2151-2604/ a000182

van Laarhoven, A.I., Vogelaar, M.L., Wilder-Smith, O.H., van Riel, P.L., van de Kerkhof, P.C., Kraaimaat, F.W., Evers, A.W. (2011). Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain 152, 1486–1494.

van Laarhoven, A.I., van der Sman-Mauriks, I.M., Donders, A.R., Pronk, M.C., van de Kerkhof, P.C., Evers, A.W. (2015). Placebo effects on itch: A meta-analysis of clinical trials of patients with dermatological conditions. J Invest Dermatol 135, 1234–1243.

Lloyd, D.M., Hall, E., Hall, S., McGlone, F.P. (2013). Can itch-related visual stimuli alone provoke a scratch response in healthy individuals? Br J Dermatol 168, 106–111.

Napadow, V., Li, A., Loggia, M., Kim, J., Schalock, P., Lerner, E., Tran, T.N., Ring, J., Rosen, B., Kaptchuk, T. (2013). Brain circuitry supporting nocebo itch perception in atopic dermatitis. Acta Derm-Venereol 93, 620.

Niemeier, V., Gieler, U. (2000). Observations during itch-inducing lecture. Dermatol Psychosom 1(suppl 1), 15–18.

Ogden, J., Zoukas, S. (2009). Generating physical symptoms from visual cues: An experimental study. Psychol Health Med 14, 695–704.

Papoiu, A.D., Wang, H., Coghill, R.C., Chan, Y.H., Yosipovitch, G. (2011). Contagious itch in humans: A study of visual 'transmission' of itch in atopic dermatitis and healthy subjects. Br J Dermatol 164, 1299–1303.

Petersen, G.L., Finnerup, N.B., Colloca, L., Amanzio, M., Price, D.D., Jensen, T.S., Vase, L. (2014). The magnitude of nocebo effects in pain: A meta-analysis. Pain 155, 1426–1434.

Pincus, T., Pearce, S., McClelland, A., Isenberg, D. (1995). Endorsement and memory bias of self-referential pain stimuli in depressed pain patients. Brit J Clin Psychol 34(Pt 2), 267–277.

Scholz, O., Hermanns, N. (1994). Illness behavior and cognitions influence the perception of itching of patients suffering from atopic dermatitis. Z Klin Psychol 23, 127–135.

Schut, C., Bosbach, S., Gieler, U., Kupfer, J. (2014). Personality traits, depression and itch in patients with atopic dermatitis in an experimental setting: A regression analysis. Acta Derm Venereol 94, 20–25.

Schut, C., Grossman, S., Gieler, U., Kupfer, J., Yosipovitch, G. (2015a). Contagious itch: What we know and what we would like to know. Front Hum Neurosci 9, 57.

Schut, C., Muhl, S., Reinisch, K., Classen, A., Jager, R., Gieler, U., Kupfer, J. (2015b). Agreeableness and self-consciousness as predictors of induced scratching and itch in patients with psoriasis. Int J Behav Med, 1–9.

Sölle, A., Bartholomäus, T., Worm, M., Klinger, R. (2014). How to psychologically minimize scratching impulses: Benefits of placebo effects on itching using classical conditioning and expectancy. Zeitschrift für Psychologie 222, 140.

Verhoeven, E.W., Kraaimaat, F.W., Jong, E.M., Schalkwijk, J., van de Kerkhof, P.C., Evers, A.W. (2009). Effect of daily stressors on psoriasis: A prospective study. J Invest Dermatol 129, 2075–2077.

Vits, S., Cesko, E., Benson, S., Rueckert, A., Hillen, U., Schadendorf, D., Schedlowski, M. (2013). Cognitive factors mediate placebo responses in patients with house dust mite allergy. PLoS ONE 8, e79576.

Wager, T.D., Atlas, L.Y., Leotti, L.A., Rilling, J.K. (2011). Predicting individual differences in placebo analgesia: Contributions of brain activity during anticipation and pain experience. J Neurosci 31, 439– 452.

Ward, J., Burckhardt, V., Holle, H. (2013). Contagious scratching: Shared feelings but not shared body locations. Front Hum Neurosci 7, 122.

Williams, J.M., Broadbent, K. (1986). Autobiographical memory in suicide attempters. J Abnorm Psychol 95, 144–149.

Williams, J.M., Ellis, N.C., Tyers, C., Healy, H., Rose, G., MacLeod, A.K. (1996). The specificity of autobiographical memory and imageability of the future. Mem Cognit 24, 116–125.

Williams, J.M., Barnhofer, T., Crane, C., Herman, D., Raes, F., Watkins, E., Dalgleish, T. (2007). Autobiographical memory specificity and emotional disorder. Psychol Bull 133, 122–148

CHAPTER 3

ROLE OF CONDITIONING AND VERBAL SUGGESTION IN PLACEBO AND NOCEBO EFFECTS ON ITCH

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Abstract

Placebo and nocebo effects are known to play a key role in treatment effects in a wide variety of conditions. These effects have frequently been investigated with regard to pain and also in other physical sensations, but have hardly been investigated with regard to itch. In addition, neither in pain nor in any other physical sensation, the single and combined contribution of the expectancy mechanisms of conditioning and verbal suggestion have ever been investigated in both placebo and nocebo effects within one design. For the first time, the role of verbal suggestion and conditioning in placebo and nocebo effects on itch was experimentally investigated. Expectations about itch stimuli were induced in healthy subjects by verbal suggestion, conditioning, or a combination of both procedures, and compared with a control group without expectation induction. Itch was induced electrically by means of quantitative sensory testing. Significant placebo and nocebo effects were induced in the group in which combined procedures of conditioning and verbal suggestion were applied in comparison with the control group. The conditioning and verbal suggestion procedures applied individually did not induce significant placebo and nocebo effects when compared with the control group. The results of this study extend existing evidence on different physical sensations, like pain, by showing that also for itch, the combination of conditioning and verbal suggestion is most promising in inducing both placebo and nocebo effects. More research on placebo and nocebo effects at a perceptive and neurobiological level is warranted to further elucidate the common and specific mechanisms underlying placebo and nocebo effects on itch and other physical sensations.

Introduction

Placebo and nocebo effects are treatment effects, unrelated to the treatment mechanism, which are induced by patients' expectations of improvement or worsening respectively [1–3]. Placebo and nocebo effects are known to contribute to the outcome of treatment effects for a range of symptoms and conditions like Parkinson's disease, gastrointestinal disorders, nausea, fatigue and pain [1,3–8]. In contrast to the extensive placebo research mainly on pain, hardly any placebo research has focused on itch, which is a common symptom of several conditions and diseases, such as dermatological and systemic diseases, and can be a considerable burden to patients especially when symptoms are chronic [9,10]. Moreover, itch particularly seems highly susceptible to suggestion, as demonstrated by the phenomenon of ''contagious'' itch: e.g., watching someone scratch himself can induce a sensation of itch in the perceiver (e.g., [11,12]). Therefore, placebo and nocebo effects might be relevant to itch in particular.

Mechanisms underlying placebo and nocebo effects have extensively been investigated, especially in the field of pain. Expectation induction mechanisms of verbal suggestion and conditioning have been identified as central processes eliciting placebo and nocebo effects, by decreasing or increasing symptoms respectively, when administering an inert (placebo) treatment or agent [2,13,14]. With regard to pain, verbal suggestion has been shown to induce short-term nocebo effects, whereas conditioning is particularly relevant to induce placebo effects and more robust nocebo effects [13,15,16]. Also in other physical sensations such as fatigue and nausea conditioning seems to be particularly relevant [5,8,17]. With regard to itch, the role of conditioning in placebo or nocebo effects has not been investigated yet, although, there is some evidence for the role of verbal suggestion in placebo and nocebo effects on itch. For example, patients with atopic dermatitis react more strongly to histamine after nocebo-related itch suggestions [18], and in a previous experiment, we showed that verbal suggestion alone can induce nocebo and possibly also placebo effects on itch [19].

Most studies investigating the role of conditioning in placebo and nocebo effects applied conditioning in combination with verbal suggestion. The few studies that used a conditioning procedure without verbal suggestion yielded mixed results [20– 23]. Hardly any research has compared the single and combined contributions of verbal suggestion and conditioning to placebo effects. Moreover, to the best of our knowledge, no direct comparison of verbal

suggestion, conditioning, and the combination of both has been made yet with regard to nocebo effects within one design.

The aim of this study was to investigate the role of verbal suggestion and conditioning in both placebo and nocebo effects on itch. Alike pain and other physical sensations, it was hypothesized that the expectation induction, particularly the combination of conditioning and verbal suggestion, would result in decreased (placebo) and increased (nocebo) itch in comparison to a control procedure. In addition, it was explored whether individual characteristics related to negative (e.g., neuroticism) or positive (e.g., optimism) outcome expectancies were associated with individual placebo and nocebo responses [13,24–27].

Methods

Ethics statement

The study was approved by the regional medical ethics committee CMO regio Arnhem-Nijmegen and follows the rules stated in the Declaration of Helsinki. All participants gave written informed consent and were reimbursed for their participation.

Participants and general procedure

Healthy subjects were recruited at the campus of the Radboud University Nijmegen, Nijmegen, the Netherlands. Exclusion criteria were severe morbidity (e.g., skin disease, multiple sclerosis, diabetes mellitus), psychiatric disorders (e.g., depression), color blindness, regular use of medication in the last 3 months, use of pacemaker, and current or past chronic itch or pain. Participants were told that the purpose of the study was to determine sensitivity to itch stimuli. At least one week prior to the experiment, a session took place in which previous experiences and expectations of sensations such as itch and pain of all subjects were assessed (results not reported here). In addition, subjects were sent self-report questionnaires about individual characteristics to be completed at home. As one subject unexpectedly went abroad after the first session, 95 subjects completed the experiment. All 95 subjects were of Dutch nationality, and were aged 18 years or older (mean age 22.7 ± 3.2 years); 77% were women. Of the subjects, 54% had a partner (13% married or living with a partner) and 58% used hormonal contraceptives. On the test day, the mean baseline levels of itch and pain were 0.5 (SD = 0.8) and 0.5 (SD = 0.7), respectively, as rated on a visual analogue scale (VAS) ranging from 0 (no itch/pain at all) to 10 (worst itch/pain ever experienced).

Test day procedure

For the test day, all subjects were asked to refrain from drinking coffee, tea, or energy drink from one hour before testing, which took place at a fixed time in the afternoon. A schematic overview of the study is displayed in Figure 1. At first, all subjects held their hands in a warm water bath at about 32°C for 3 minutes [28], in order to attain a comparable baseline wrist skin temperature among participants. Then the itch thresholds were determined by gradually increasing the intensity of the electric current with a ramping procedure (see Methods; Itch induction). Thereafter, subjects were randomly assigned to one of four groups, using a computer generated randomization list. Since the instructions given to the subjects differed in accordance with the group the subjects were allocated to, only subjects were blinded for the randomization to different groups. In line with previous conditioning studies of nocebo and placebo effects on pain [15,16], the experimental session comprised two phases: a learning phase and a testing phase. In both phases, itch stimuli were preceded by visual cues (colored lights, i.e., green, yellow, and red lights) displayed on a computer screen. The learning phase consisted of two blocks, in which either no expectations were induced or participants received verbal suggestion, conditioning, or a combination of both procedures, to induce expectations about the intensity of the itch stimuli. In this phase, itch stimuli of a varying intensity were applied, preceded by a cue (6x green, 6x yellow, and 6x red cue). In the testing phase, itch stimuli were all applied at medium intensity, preceded by a cue (5x green, 5x yellow, and 5x red cue). After the threshold measurements and in-between the different experimental blocks, there was a standardized 10-minute break in which participants were provided with a selected number of magazines to read with a neutral content (about nature and home decoration), and they were offered a small snack and herbal tea or water (see also Fig. 1)

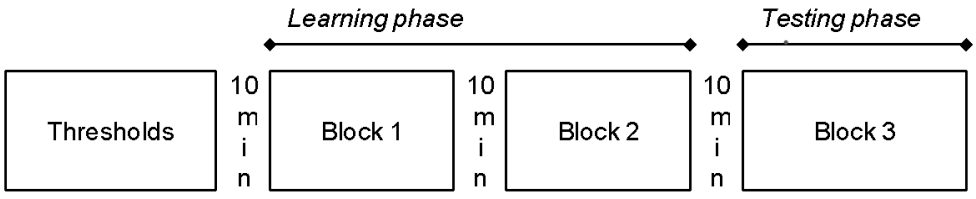

Figure. 1. Flow diagram showing the experimental procedures of the study in chronological order.

Experimental groups and control group

The experimental design is displayed in Figure 2. In the verbal suggestion group, expectations of low, neutral, and high levels of itch were raised in subjects by telling them that different cues (colored lights on the computer screen) indicated that the stimulus intensity would be altered. This change would be brought about by a third electrode, which was actually a placebo or sham electrode (inactive electrode): ''A green light will signal the activation of the third electrode that induces a decrease in the intensity of the itch stimulus. A red light will signal an increase in the intensity of the itch stimulus by the activation of the electrode, and the yellow light will indicate that the third electrode is turned off and will not change the intensity of the itch stimulus''. Regardless of the color of the cue displayed, all stimuli had a medium intensity. In the conditioning group, expectations of low, neutral, and high levels of itch were raised in subjects by the repeated pairing of the green, yellow, and red cues with low, medium, and high itch stimulus intensities, respectively. The current intensities (mA) for the low, medium, and high stimulus intensities were determined according to the participants' individual itch thresholds (see Methods; itch induction). No verbal suggestion was given to avoid any verbal suggestion effects, i.e., subjects were not given information about the stimulus intensity, but were merely told that several itch stimuli would be applied after the presentation of color cues. In the conditioning with verbal suggestion group, the conditioning procedure and the verbal suggestion procedure were combined, thus applying stimuli of low, medium, and high intensity concurrently with the green, yellow, and red cues, respectively, and the corresponding verbal suggestion. In the control group, no expectations regarding the itch stimuli were induced, neither by verbal suggestion nor by conditioning, i.e., subjects were not given information about the colored cues or stimulus intensity, and itch stimuli were given independently of the colored cue at a predetermined random order at low, medium, and high intensity. Unlike in the learning phase, in the testing phase only stimuli of medium intensity were applied in all groups. The verbal suggestion given in the testing phase corresponded with the verbal suggestion given in the learning phase (See Fig. 2. for the experimental design).

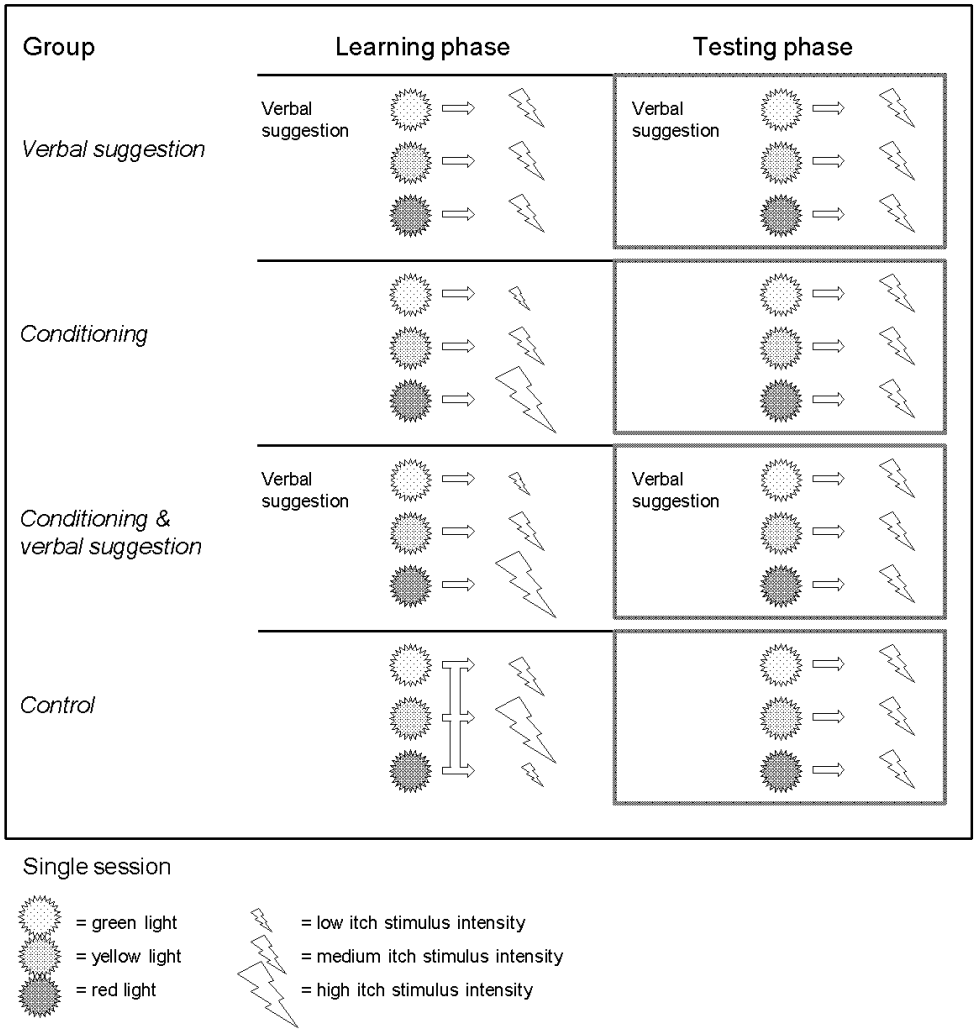

Figure. 2. Experimental design. Subjects were randomly assigned to one of four groups: verbal suggestion; conditioning; verbal suggestion with conditioning; and control. In the learning phase verbal suggestion and conditioning procedures depended on the experimental group. In the testing phase the verbal suggestion was in correspondence with the verbal suggestion applied in the learning phase, while all participants received itch stimuli of a medium intensity.

Itch induction

Itch was induced by means of electrical stimulation by a constant current stimulator (Isolated Bipolar Constant Current Stimulator DS5, Digitimer, United Kingdom), and delivered to the inner side of the non-dominant wrist through two surface electrodes (a disk electrode of ø 1 cm and a reference electrode of ø 2 cm, VCM Medical, the Netherlands). The stimulator

was coupled to a data acquisition system (NI-DAQmx, National Instruments, Hungary), which was controlled by a laptop. One electrode was applied 1.5 cm proximal to the triquetrum, at the center of the inner wrist, while the reference electrode was applied 2 cm below. A third (sham) electrode was placed about 1 cm left from the two real electrodes and attached to the back of the stimulator. Stimuli were applied at 50-Hz frequency with a pulse duration of 100 μs [29] and at a continuously increasing current intensity (0.05 mA/s) up to a maximum current intensity of 5 mA. After each stimulus, participants were asked to report the level of itch on a visual analogue scale (VAS) ranging from 0 (no itch at all) to 10 (worst itch ever experienced). The following thresholds were measured three times by gradually increasing the current intensity from 0 mA up to the intensity at which the respective threshold had been reached: ''the first moment you feel some itch'' (IT1); ''the first moment you feel the urge to scratch'' (IT2); and ''the first moment you cannot resist the urge to scratch'' (IT3). The mean of these thresholds was used for the calculation of the individual current intensities of the low, medium, and high itch stimulus applied in the experimental phase. In-between every stimulus applied in the learning and testing phase, there was a 2-minute interval, in which filler tasks (e.g., puzzles) were given to diminish possible influence of itch evoked by previously applied stimuli on subsequent stimuli. The interval could be extended to a maximum of 4 minutes if the level of itch after 2 minutes was ≥2 on a VAS.

Questionnaires

Individual psychological characteristics of optimism, hope, neuroticism, extraversion, negative affect and worrying were assessed by means of self-report questionnaires, previously shown to have satisfactory reliability and validity.

Optimism

The Revised Life Orientation Test (LOT-R) [30] was used to measure optimism, the tendency to expect positive outcomes. The LOT-R consists of 10 items scored on a 5-point Likert scale ranging from 0 (''Strongly Disagree'') to 4 (''Strongly Agree''). Total scores range from 0 to 24, with higher scores indicating higher levels of dispositional optimism. In the present study, Cronbach's alpha was 0.79.

Hope

The Dispositional Hope Scale (DHS) was used to measure hope, the tendency to experience a reciprocally derived sense of successful agency and pathways [31,32]. The DHS

consist of 12 items scored on a 8-point Likert scale ranging from 1 (''Definitely False'') to 8 (''Definitely true''), with higher scores indicating higher levels of hope. In the present study, Cronbach's alpha was 0.78.

Neuroticism & Extraversion

The Eysenck Personality Questionnaire (EPQ) was used to measure neuroticism, the tendency to experience more negative affect and negative outcome expectations, and extraversion, the tendency of having more outgoing, talkative, and energetic behavior [33]. The neuroticism and extraversion subscales consist of 22 and 19 ''yes/no'' items, respectively. Higher scores indicate higher levels of neuroticism and extraversion. In the present study, Cronbach's alpha was 0.84 for neuroticism and 0.86 for extraversion.

Negative affect

The Hospital Anxiety and Depression Scale (HADS) was used to measure negative affect characterized by symptoms of depression and anxiety [34]. The HADS consists of 14 items scored on a 4-point Likert scale ranging from 0 (''no problem'') to 3 (''severe problem''), with higher scores indicating higher levels of negative affect. In the present study, Cronbach's alpha was 0.80.

Worrying

The Penn State Worry Questionnaire (PSWQ) [35] was used to measure worrying, which includes the tendency to experience more negative outcome expectancies. The PSWQ consists of 16 items scored on a 5-point Likert scale, ranging from 1 (''not at all typical of me'') to 5 (''very typical of me''), with higher scores indicating greater worrying. In the present study, Cronbach's alpha was 0.93.

Statistical analysis

All analyses were performed using SPSS 20.0 for Windows (SPSS Inc. Chicago, Illinois, USA). Analyses of variance (ANOVA) and Chi-square tests were used to test for baseline differences in demographic variables between the four groups. Means of the VAS itch scores were calculated for the learning and testing phases in all groups. Variables were checked for outliers and skewness as these can severely limit the usefulness of the mean as measure for location. Since there was no indication of problems in this respect, untransformed variables were analyzed. In order to be able to measure nocebo and placebo effects, i.e., by an increase or a decrease in itch respectively, an intermediate itch intensity was introduced by applying a

stimulus at medium intensity preceded by a yellow cue along with a neutral expectation. The nocebo effect was then defined as the difference between the mean itch VAS scores associated with the five red cues and the five yellow cues in the testing phase, and the placebo effect was defined as the difference between the mean itch VAS scores associated with the five green cues and the five yellow cues in the testing phase. Univariate analyses of variance (ANOVAs) were performed with group as between-subject factor for nocebo and placebo effects, in order to test the hypothesis, i.e., that the experimental groups would display significant nocebo and placebo effects in comparison with the control group. Post hoc Dunnett tests were conducted to compare the experimental groups separately with the control group. The effectiveness of the expectation induction procedures was also exploratively assessed during the learning phase. Again, separate ANOVAs and post hoc Dunnett tests were performed as described above, exploring the difference in itch VAS scores between the green- or red- and yellow-associated stimuli in the learning phase. Exploratively, in the three experimental groups Pearson correlation coefficients were calculated between the nocebo and placebo effects and questionnaire scores for individual characteristics. For all analyses, the level of statistical significance was set at $p<0.05$.

Results

Experimental and control groups

Randomization of the subjects across the different experimental and control groups resulted in a total of 23 subjects in the verbal suggestion group, 24 subjects in the conditioning group, 23 subjects in the conditioning with verbal suggestion group, and 25 subjects in the control group. There were no significant between-group differences with regard to age, gender, use of hormonal contraceptives, and baseline levels of itch and pain on the test day.

Nocebo effects

Learning phase for induction of nocebo effects. Table 1 displays the mean (±SD) itch VAS scores evoked by the stimuli associated with the red and yellow cues during the learning phase for the four groups. When exploring whether the difference in the levels of electrically evoked itch (i.e., red minus yellow cue) would be larger in the three experimental groups than in the control group, Univariate analysis of variance (ANOVA) revealed a significant between group effect ($F(3,91) = 49.528$, $p<0.001$). Post hoc Dunnett tests indicated a significantly larger itch

VAS difference score between the red- and yellow-associated stimuli, for the verbal suggestion group ($p<0.001$), the conditioning group ($p<0.001$) and the conditioning with verbal suggestion group ($p<0.001$) as compared with the control group.

Table 1. Means and standard deviations for itch VAS scores in the learning phase for the different groups

	Itch VAS scores (M ± SD)		
Group	Green cue	Yellow cue	Red cue
Verbal suggestion	4.56 ± 1.81	4.77 ± 1.78	5.39 ± 1.83
Conditioning	3.73 ± 2.07	4.54 ± 2.09	5.84 ± 2.01
Conditioning & Verbal suggestion	2.37 ± 1.75	3.97 ± 1.34	6.04 ± 1.55
Control	3.52 ± 2.00	3.43 ± 2.01	2.87 ± 1.68

Means (M) and standard deviations (SD) of the visual analogue scale (VAS) scores for itch in the verbal suggestion group (*n = 23*), conditioning group (*n = 24*), conditioning with verbal suggestion group (*n = 23)* and control group (*n = 25*) in the learning phase.

Testing phase nocebo effects. Table 2 displays the mean (±SD) itch VAS scores evoked by the stimuli associated with the red and yellow cues during the testing phase for each group (in which all stimuli were applied at medium intensity), and the mean nocebo effect for each group is shown in Figure 3. Univariate ANOVA showed a significant difference in the magnitude of the nocebo effect in the different groups ($F(3,91) = 2.995$, $p = 0.035$). Post hoc Dunnett tests comparing the experimental groups with the control group indicated a significant nocebo effect in the conditioning with verbal suggestion group ($p = 0.020$), a borderline significant nocebo effect in the verbal suggestion group ($p = 0.063$), and no significant nocebo effect in the conditioning group when compared with the control group (See Fig. 3.).

Table 2. Means and standard deviations for itch VAS scores in the testing phase for the different groups

	Itch VAS scores (M ± SD)		
Group	Green cue	Yellow cue	Red cue
Verbal suggestion	3.20 ± 1.91	3.60 ± 1.91	3.87 ± 2.05
Conditioning	3.30 ± 1.87	3.41 ± 1.80	3.59 ± 1.87
Conditioning & Verbal suggestion	2.42 ± 1.68	3.28 ± 1.71	3.65 ± 2.00
Control	2.33 ± 1.62	2.65 ± 1.87	2.38 ± 1.70

Means (M) and standard deviations (SD) of the visual analogue scale (VAS) scores for itch in the verbal suggestion group (*n = 23*), conditioning group (*n = 24*), conditioning with verbal suggestion group (*n = 23*), and control group (*n = 25*) in the testing phase.

Placebo effects

Learning phase for induction of placebo effects. Table 1 displays the means and standard deviations (SD) of the itch VAS scores evoked by the stimuli associated with the green and yellow cues during the learning phase for the four groups. When exploring whether the difference in the levels of electrically evoked itch (i.e., yellow minus green cue) would be larger in the three experimental groups than in the control group, Univariate analysis of variance (ANOVA) revealed a significant group effect ($F(3,91) = 16.742$, $p<0.001$). Post hoc Dunnett tests indicated a significantly larger itch VAS difference score between the green-and yellow-associated stimuli, for the conditioning group ($p = 0.002$) and the conditioning with verbal suggestion group ($p<0.001$), as compared with the control group. In the comparison to the control group, the verbal suggestion group did not differ in itch VAS difference score between the green- and yellow-associated stimuli.

Testing phase placebo effects. Table 2 displays the mean (±SD) itch VAS scores evoked by the stimuli associated with the green and yellow cues during the testing phase for each group (in which all stimuli were applied at medium intensity), and the mean placebo effect for each group is shown in Figure 4. Univariate ANOVA showed a significant difference in the magnitude of the placebo effect in the different groups ($F (3,91) = 6.154$, $p = 0.001$). Post hoc Dunnett tests comparing the experimental groups with the control group indicated a significant placebo effect in the conditioning with verbal suggestion group ($p = 0.009$), but no

significant differences in the placebo effect were found in the verbal suggestion group or the conditioning group when compared with the control group (See Fig. 4.).

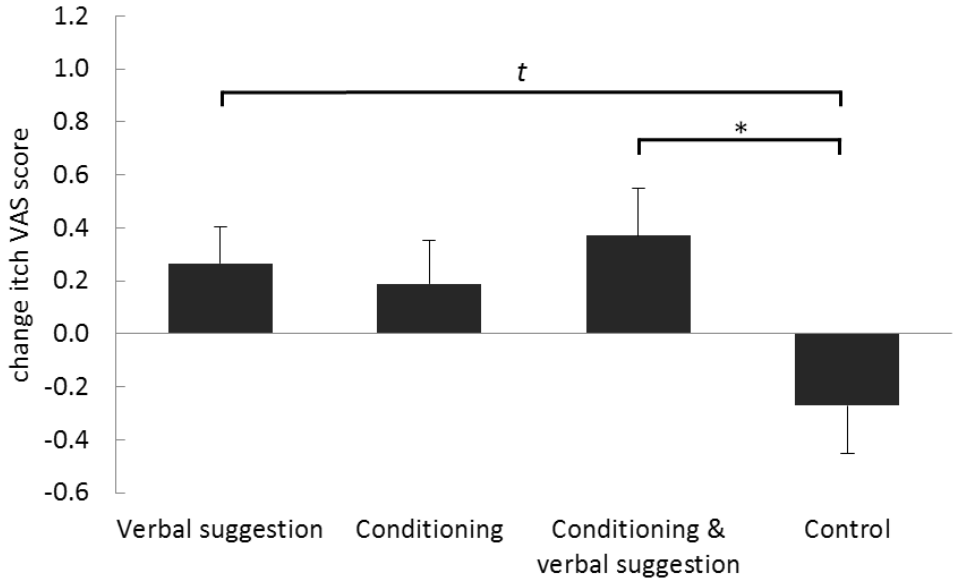

Figure. 3. Means and standard error of the mean of the visual analogue scale (VAS) itch scores for the nocebo effect (change VAS score between the red and yellow cues) of the four groups in the testing phase. The asterisks show the level of significance related to the post hoc Dunnett comparison of the nocebo effect between the experimental groups and the control group (**$p < 0.01$; *$p < 0.05$; $t = p < 0.10$).

Individual characteristics

Nocebo effect. In the conditioning with verbal suggestion group, significant correlation coefficients were found between a greater nocebo response and more worrying (r = 0.485; p = 0.019), more negative affect (r = 0.433; p = 0.039), less hope (r = –0.452; p = 0.030), and lower levels of extraversion (r = –0.511; p = 0.013), but not with neuroticism or optimism. No significant correlations were found in the other experimental groups.

Placebo effect. The magnitude of the placebo effect was not significantly correlated with the individual characteristics of optimism, hope, extraversion, neuroticism, negative affect, and worrying in any of the three experimental groups, except for a significant correlation coefficient between a greater placebo effect and less hope in the conditioning with verbal suggestion group (r = –0.507; p = 0.014).

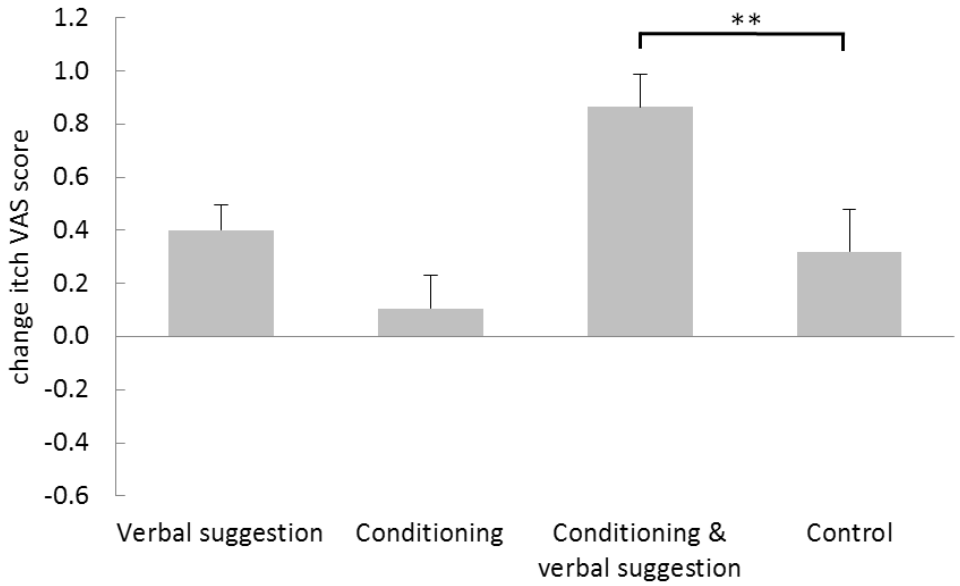

Figure. 4. Means and standard error of the mean of the visual analogue scale (VAS) itch scores for the placebo effect (change VAS score between the green and yellow cues) of the four groups in the testing phase. The asterisks show the level of significance related to the post hoc Dunnett comparison of the placebo effect between the experimental groups and the control group (**$p < 0.01$; *$p < 0.05$; $t = p < 0.10$).

Discussion

For the first time, expectation induction procedures of verbal suggestion, conditioning and the combination of both were investigated with regard to both nocebo and placebo effects on itch. Results show that nocebo and placebo effects can be induced on itch, with the strongest effects elicited by a combination of conditioning and verbal suggestion rather than by either procedure alone. These results are in line with research in nocebo and placebo effects on pain and other physical sensations such as nausea and fatigue (e.g., [5,8,13,15]).

The subjects receiving both conditioning and verbal suggestion procedures had significantly higher (nocebo) and lower (placebo) levels of induced itch than did the subjects receiving the control procedure. Additional support for these findings was found in the learning phase, during which there was a similar pattern of changes in itch VAS scores in response to nocebo and placebo cues. These findings are consistent with earlier research on

pain which showed that the combination of conditioning and verbal suggestion evoked robust hyperalgesic and analgesic effects [13,15,36]. Moreover, when verbal suggestion procedures were combined with conditioning, generally larger and longer-lasting nocebo and placebo effects could be induced when compared with these procedures alone [13,15,20,22,23,36,37]. In addition, also in other physical symptoms further support has been found for the combination of conditioning and verbal suggestion such as in nausea and fatigue [5,38]. For inducing nocebo and placebo effects on various physical sensations, the combination of these expectation induction mechanisms seems most promising.

Verbal suggestion (without conditioning) elicited a marginally significant nocebo effect on itch when compared with a control procedure during the testing phase, and elicited a robust significant nocebo effect in the learning phase. Previous research has shown that robust nocebo effects on itch [19] and pain [1,2,13,14] can be induced by verbal suggestion. In contrast, placebo effects were not significantly induced by verbal suggestion when compared with a control procedure, i.e., subjects did not experience less itch when told that the stimulus would evoke less itch, than when given neutral suggestions (control group). However, indirect indications were found for a placebo effect within the verbal suggestion group by showing that these subjects experienced significantly lower levels of itch for the stimuli associated with the green (placebo) versus the yellow (neutral) cues (see table 2). Using two phases (learning and testing phase) might have led to extinction of effects that were present in the first (learning) phase, while to test for the effects of verbal suggestion a single phase is sufficient [15].

Conditioning (without verbal suggestion) did not elicit significant nocebo or placebo effects on itch in the testing phase (in which all itch stimuli were of the same intensity). This finding was somewhat unexpected since significant altered itch scores were present in the learning phase. A reason for non-significant effects of conditioning might be the number or length of learning trials. The few previous studies that investigated the effects of conditioning (without verbal suggestion) on pain generally found significant nocebo or placebo effects for example when more or longer lasting learning trials were used [20–23]. During conditioning, the perception of an increase or decrease in sensations after a cue can shape both automatic and conscious expectations about the given cue [39], and with more or longer conditioning trials, the learned association may be more predictable. Moreover, the addition of explicit

expectations (by verbal suggestion) might further amplify the induction of nocebo and placebo effects on physical sensations, and itch in particular which seems highly susceptible to suggestion as demonstrated by the phenomenon of ‘‘contagious’’ itch (e.g., [11,12]).

Individual characteristics related to outcome expectancies were, in contrast to the placebo effect, associated with the nocebo effect (more negative affect, less extraversion, more neuroticism and less hope). This is in line with previous findings on nocebo effects [13,24–27], and studies showing that particularly negative affect and cognitions can enhance itch [19,40–43]. These findings also support the idea that negative (aversive responses) rather than positive (safety responses) expectations may be easier to induce from an evolutionary perspective in order to promote survival [15,44], possibly mediated by a tendency to experience more negative affect and cognitions, such as worrying. These findings also underline the possibly divergent mechanisms underlying nocebo and placebo effects. While anxiety or stress-related processes are thought to be involved in nocebo hyperalgesia, e.g., through an increase in cortisol plasma concentrations, reward processes are supposed to be involved in placebo analgesia, e.g., by the activation of dopamine neurotransmission [39,45]. Additional research into the possible predictors and different mechanisms of nocebo and placebo responding is clearly required.

Some limitations and implications for future research should be discussed. First, the number of conditioning trials in the learning phase might have been insufficient to induce nocebo or placebo effects in the group receiving conditioning alone (i.e., without verbal suggestion) [20–22]. Second, placebo effects were not only found in the experimental groups, as expected, but also in the control group there was a tendency for a decrease in itch (see table 2). The expectations of the participants regarding the visual stimuli may have unintentionally been influenced because, during the random allocation of cues to a stimulus intensity, the yellow cue was more often (than by chance) associated with a high intensity itch stimulus. This could, for example, explain the lack of a significant placebo effect in the verbal suggestion group in relation to the control group. Third, in contrast to previous studies investigating the role of either negative or positive expectations on itch [18,19,46], in this study we induced nocebo and placebo expectations at the same time in individual participants. Since different mechanisms may underlie the induction of nocebo and placebo effects, this might have tempered the magnitude of the effects. Fourth, the subjects’

expectations regarding the colored cues were not assessed explicitly; so that we cannot exclude that other mechanisms than expectancy effects might be responsible for the placebo and nocebo effects found in this study. Lastly, knowledge of nocebo and placebo effects on itch may, in the long term, help improve therapeutic interventions by reducing unfavorable expectations and enhancing favorable expectations in patients suffering from chronic itch. It remains to be established whether the findings of experimentally induced sensations in healthy subjects can be generalized to patients in a clinical setting. Moreover, the role of individual characteristics in nocebo and placebo responsiveness should be elucidated to further personalize interventions and to optimize treatment outcomes.

In conclusion, this study showed that, in accordance with research on other physical sensations, the combination of conditioning and verbal suggestion can induce significant nocebo and placebo effects on itch. Research on nocebo and placebo effects at a perceptive and neurobiological level is warranted to further elucidate the common and specific mechanisms underlying nocebo and placebo effects on itch and other physical sensations.

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References

Benedetti F (2008) Mechanisms of placebo and placebo-related effects across diseases. Annual Review of Pharmacology and Toxicology 48: 33–60.

Colloca L, Miller FG (2011) The nocebo effect and its relevance for clinical practice. Psychosom Med 73: 598–603.

Price DD, Finniss DG, Benedetti F (2008) A comprehensive review of the placebo effect: Recent advances and current thought. Annual Review of Psychology 59: 565–590.

Enck P, Bingel U, Schedlowski M, Rief W (2013) The placebo response in medicine: minimize, maximize or personalize? Nat Rev Drug Discov 12: 191– 204.

Horing B, Weimer K, Schrade D, Muth ER, Scisco JL, et al. (2013) Reduction of motion sickness with an enhanced placebo instruction: an experimental study with healthy participants. Psychosom Med 75: 497–504.

Lee HF, Hsieh JC, Lu CL, Yeh TC, Tu CH, et al. (2012) Enhanced affect/ cognition-related brain responses during visceral placebo analgesia in irritable bowel syndrome patients. Pain 153: 1301–1310.

Musial F, Klosterhalfen S, Enck P (2007) Placebo responses in patients with gastrointestinal disorders. World J Gastroenterol 13: 3425–3429.

Pollo A, Carlino E, Benedetti F (2008) The top-down influence of ergogenic placebos on muscle work and fatigue. Eur J Neurosci 28: 379–388.

Schneider G, Driesch G, Heuft G, Evers S, Luger TA, et al. (2006) Psychosomatic cofactors and psychiatric comorbidity in patients with chronic itch. Clin Exp Dermatol 31: 762–767.

Verhoeven EW, de Klerk S, Kraaimaat FW, van de Kerkhof PC, de Jong EM, et al. (2008) Biopsychosocial mechanisms of chronic itch in patients with skin diseases: a review. Acta Derm Venereol 88: 211–218.

Holle H, Warne K, Seth AK, Critchley HD, Ward J (2012) Neural basis of contagious itch and why some people are more prone to it. Proc Natl Acad Sci U S A 109: 19816–19821.

Papoiu AD, Wang H, Coghill RC, Chan YH, Yosipovitch G (2011) Contagious itch in humans: a study of visual 'transmission' of itch in atopic dermatitis and healthy subjects. Br J Dermatol 164: 1299–1303.

Colloca L, Klinger R, Flor H, Bingel U (2013) Placebo analgesia: Psychological and neurobiological mechanisms. Pain 154: 511–514.

Benedetti F, Amanzio M (2011) The placebo response: How words and rituals change the patient's brain. Patient Educ Couns 84: 413–419.

Colloca L, Sigaudo M, Benedetti F (2008) The role of learning in nocebo and placebo effects. Pain 136: 211–218.

Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F (2010) How the number of learning trials affects placebo and nocebo responses. Pain 151: 430– 439.

Klosterhalfen S, Ruttgers A, Krumrey E, Otto B, Stockhorst U, et al. (2000) Pavlovian conditioning of taste aversion using a motion sickness paradigm. Psychosom Med 62: 671–677.

Scholz O, Hermanns N (1994) Illness behavior and cognitions influence the perception of itching of patients suffering from atopic dermatitis. Z Klin Psychol 23: 127–135.

van Laarhoven AI, Vogelaar ML, Wilder-Smith OH, van Riel PL, van de Kerkhof PC, et al. (2011) Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain 152: 1486–1494.

Martin-Pichora AL, Mankovsky-Arnold TD, Katz J (2011) Implicit versus explicit associative learning and experimentally induced placebo hypoalgesia. J Pain Res 4: 67–77.

Jensen KB, Kaptchuk TJ, Kirsch I, Raicek J, Lindstrom KM, et al. (2012) Nonconscious activation of placebo and nocebo pain responses. Proc Natl Acad Sci U S A 109: 15959–15964.

Voudouris NJ, Peck CL, Coleman G (1990) The role of conditioning and verbal expectancy in the placebo response. Pain 43: 121–128.

Amanzio M, Benedetti F (1999) Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. J Neurosci 19: 484–494.

Pecina M, Azhar H, Love TM, Lu T, Fredrickson BL, et al. (2013) Personality trait predictors of placebo analgesia and neurobiological correlates. Neuropsy-chopharmacology 38: 639–646.

Geers AL, Helfer SG, Kosbab K, Weiland PE, Landry SJ (2005) Reconsidering the role of personality in placebo effects: dispositional optimism, situational expectations, and the placebo response. J Psychosom Res 58: 121–127.

Geers AL, Kosbab K, Helfer SG, Weiland PE, Wellman JA (2007) Further evidence for individual differences in placebo responding: an interactionist perspective. J Psychosom Res 62: 563–570.

Morton DL, Watson A, El-Deredy W, Jones AK (2009) Reproducibility of placebo analgesia: Effect of dispositional optimism. Pain 146: 194–198.

Mitchell LA, MacDonald RA, Brodie EE (2004) Temperature and the cold pressor test. The J Pain 5: 233–237.

Ikoma A, Handwerker H, Miyachi Y, Schmelz M (2005) Electrically evoked itch in humans. Pain 113: 148–154.

Scheier MF, Carver CS, Bridges MW (1994) Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol 67: 1063–1078.

Snyder CR, Harris C, Anderson JR, Holleran SA, Irving LM, et al. (1991) The will and the ways: Development and validation of an individual-differences measure of hope. J Pers Soc Psychol 60: 570–585.

Brouwer D, Meijer RR, Weekers AM, Baneke JJ (2008) On the dimensionality of the Dispositional Hope Scale. Psychol Assess 20: 310–315.

Eysenck HJ, Eysenck SBG (1975) EPQ (Eysenck Personality Questionnaire): Educational and Industrial Testing Service.

Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67: 361–370.

Meyer TJ, Miller ML, Metzger RL, Borkovec TD (1990) Development and validation of the Penn State worry questionnaire. Behav Res Ther 28: 487–495.

Klinger R, Soost S, Flor H, Worm M (2007) Classical conditioning and expectancy in placebo hypoalgesia: a randomized controlled study in patients with atopic dermatitis and persons with healthy skin. Pain 128: 31–39.

Colloca L, Benedetti F (2006) How prior experience shapes placebo analgesia. Pain 124: 126–133.

Pollo A, Carlino E, Benedetti F (2008) The top-down influence of ergogenic placebos on muscle work and fatigue. Eur J Neurosci 28: 379–388.

Atlas LY, Wager TD (2012) How expectations shape pain. Neuroscience Letters 520: 140–148.

Evers AW, Verhoeven EW, Kraaimaat FW, de Jong EM, de Brouwer SJ, et al. (2010) How stress gets under the skin: cortisol and stress reactivity in psoriasis. Br J Dermatol 163: 986–991.

Verhoeven EW, Kraaimaat FW, de Jong EM, Schalkwijk J, van de Kerkhof PC, et al. (2009) Individual differences in the effect of daily stressors on psoriasis: a prospective study. Br J Dermatol 161: 295–299.

Verhoeven EW, Kraaimaat FW, Jong EM, Schalkwijk J, van de Kerkhof PC, et al. (2009) Effect of daily stressors on psoriasis: a prospective study. J Invest Dermatol 129: 2075–2077.

van Laarhoven AI, Walker AL, Wilder-Smith OH, Kroeze S, van Riel PL, et al. (2012) Role of induced negative and positive emotions in sensitivity to itch and pain in women. Br J Dermatol 167: 262–269.

Vlaeyen JW, Linton SJ (2000) Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain 85: 317–332.

Benedetti F, Carlino E, Pollo A (2011) How Placebos Change the Patient's Brain. Neuropsychopharmacology 36: 339–354.

Niemeier V, Gieler U (2000) Observations during Itch-Inducing Lecture. Dermatology and Psychosomatics/Dermatologie und Psychosomatik (suppl 1): 15–18.

CHAPTER 4

MINIMIZING NOCEBO EFFECTS BY CONDITIONING WITH VERBAL SUGGESTION: A RANDOMIZED CLINICAL TRIAL IN HEALTHY HUMANS

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Abstract

Nocebo effects, i.e., adverse treatment effects which are induced by patients' expectations, are known to contribute to the experience of physical symptoms such as pain and itch. A better understanding of how to minimize nocebo responses might eventually contribute to enhanced treatment effects. However, little is known about how to reduce nocebo effects. In the current randomized controlled study, we tested whether nocebo effects can be minimized by positive expectation induction with respect to electrical and histaminic itch stimuli. First, negative expectations about electrical itch stimuli were induced by verbal suggestion and conditioning (part 1: induction of nocebo effect). Second, participants were randomized to either the experimental group or one of the control groups (part 2: reversing nocebo effect). In the experimental group, positive expectations were induced by conditioning with verbal suggestion. In the control groups either the negative expectation induction was continued or an extinction procedure was applied. Afterwards, a histamine application test was conducted. Positive expectation induction resulted in a significantly smaller nocebo effect in comparison with both control groups. Mean change itch NRS scores showed that the nocebo effect was even reversed, indicating a placebo effect. Comparable effects were also found for histamine application. This study is the first to demonstrate that nocebo effects can be minimized and even reversed by conditioning with verbal suggestion. The results of the current study indicate that learning via counterconditioning and verbal suggestion represents a promising strategy for diminishing nocebo responses.

Introduction

Nocebo effects, i.e., adverse treatment effects which are induced by patients' expectations, play a central role in clinical practice [1, 2]. For example, patients receiving placebos in placebo-controlled clinical trials often report side effects similar to those experienced by patients receiving the active treatment [2]. These effects may be merely attributed to oral and written communication about potential adverse side effects in the informed consent procedure. Similarly, nocebo-induced side effects can also occur in response to an active treatment; this response can affect patients' adherence and lead to withdrawal from necessary treatment [3]. Moreover, negative expectations regarding a certain treatment may reduce treatment effectiveness itself. For example, when patients are given an analgesic drug, positive expectations regarding its effects can double the effect, whereas negative expectations can completely abolish the analgesic effect [4]. A greater understanding of nocebo effects and how to diminish them is important for discovering ways of reducing their contribution to itch and other physical symptoms in clinical practice.

While most studies on nocebo effects derive from the field of pain, nocebo effects are also known to play a role in a range of other symptoms and conditions, such as gastrointestinal disorders, nausea, fatigue, allergic symptoms, and itch [5, 6][7]. Itch, like pain, is a common and severe symptom of several conditions and diseases, such as dermatological and systemic diseases, and can be a significant burden to patients, particularly when symptoms are chronic [8–11]. Chronic itch is associated with, for instance, lower quality of life, impairment of sleep, feelings of stigmatization, and depressive symptoms [9, 10]. Itch seems particularly susceptible to suggestion. This is demonstrated by the phenomenon of contagious itch–e.g., watching someone scratch himself can induce a sensation of itch in the perceiver [12, 13]–and by several recent studies demonstrating the role of nocebo effects on itch [14–17], by which nocebo effects might even be larger than in pain [14]. This makes itch a useful model to investigate the expectancy learning in nocebo effects.

With regard to expectancy learning in nocebo effects, the two expectation induction procedures that have been investigated most frequently are verbal suggestion and conditioning. Verbal suggestion consists of providing verbal or written information about clinical improvement or aggravation, such as potential side effects [18]. Conditioning, on the other hand, consists of repeatedly pairing a neutral stimulus (e.g., visual stimulus) with an

active ingredient (e.g., increased pain stimulus), so that in time the neutral stimulus comes to elicit a similar response as the innate response (e.g., heightened experience of pain) [18]. Numerous studies have found evidence that verbal suggestion, conditioning and especially the combination of conditioning with verbal suggestion can induce nocebo effects on physical symptoms [15, 19–21]. As far as we know, only one study investigated whether nocebo-like effects can be reduced, using verbal suggestion procedures [22]. Reduction of nocebo effects, particularly induced via conditioning, has so far not been explored.

Changing of conditioned effects has been studied in fear and evaluative conditioning paradigms in particular [23–26]. Two main procedures that are used to change conditioned effects are extinction and counterconditioning. During extinction, a conditioned stimulus (CS) that was previously paired with e.g., a negative unconditioned stimulus (US) is now presented without the US. During counterconditioning, the CS-US pairing is still presented but the valence of the US is now opposite to the valence of the US with which it was previously paired (e.g., positive vs. negative) [23, 27–30]. Although extinction has been studied extensively, the results are mixed. Counterconditioning, on the other hand, has been investigated less frequently, but results show quite consistently that it can effectively change conditioned effects [25, 26, 31]. Counterconditioning has yet not been investigated with regard to nocebo (or placebo) effects, but could, in combination with verbal suggestion, prove an effective procedure to reduce nocebo effects.

In the present study we aimed to investigate whether conditioned nocebo responses to itch could be reduced by a positive expectation induction. Healthy participants were first exposed to a negative expectation induction (nocebo effect induction) by a procedure that combined conditioning and verbal suggestion regarding electrical itch stimuli. Then they were exposed to a positive expectation induction by a procedure that combined counterconditioning and verbal suggestion (placebo effect induction). In line with studies on counterconditioning e.g., [25, 32], control groups consisted of continued negative expectation inductions or an extinction procedure. It was hypothesized that the positive expectation induction would result in decreased itch in comparison with the two control groups. In addition, we exploratively tested the extent to which previously reduced nocebo effects would generalize to a different itch stimulus to assess external validity. Furthermore, it was explored whether psychological characteristics related to negative or positive outcome expectancies

(e.g., worrying or optimism, respectively) were associated with (reversion of) nocebo responses [15, 33].

Methods

Ethics statement

The study was approved by the medical ethics committee of the Leiden University Medical Center in Leiden, the Netherlands (Commissie Medische Ethiek) and follows the rules stated in the Declaration of Helsinki. The study was registered retrospectively at the ISRCTN registry (registration code: ISRCTN 76895197), since this is a randomized experimental lab study in healthy individuals. The authors confirm that all ongoing and related trials for this intervention are registered. All participants gave written informed consent and were reimbursed for participation.

Participants

In total 129 participants were included in this study. Exclusion criteria were severe physical morbidity (e.g., skin disease, diabetes mellitus, multiple sclerosis), psychiatric disorders (e.g., depression), chronic itch or pain complaints, diagnosis of histamine hypersensitivity, regular use of medication in the last 3 months, use of a pacemaker, and color blindness. All participants were of Dutch nationality, and were aged 18 years or older (mean age 20.25 ± 2.46 years; 78.7% were women.

Design

This study used a balanced (1:1:1) randomized, multi-arm parallel-group, single blind design. The study comprised three parts: in the first part, all participants received a negative expectation induction regarding electrical itch stimuli (induction nocebo effect; part 1); in the second part, participants were equally randomized over three experimental groups in which they either received a positive expectation induction (induction placebo effect; group 1), a continued negative expectation induction (induction nocebo effect; group 2), or an extinction procedure (extinction; group 3). In the third part, generalization of reduced nocebo effects to another itch stimulus, histamine iontophoresis, was tested. Fig 1. displays the experimental design.

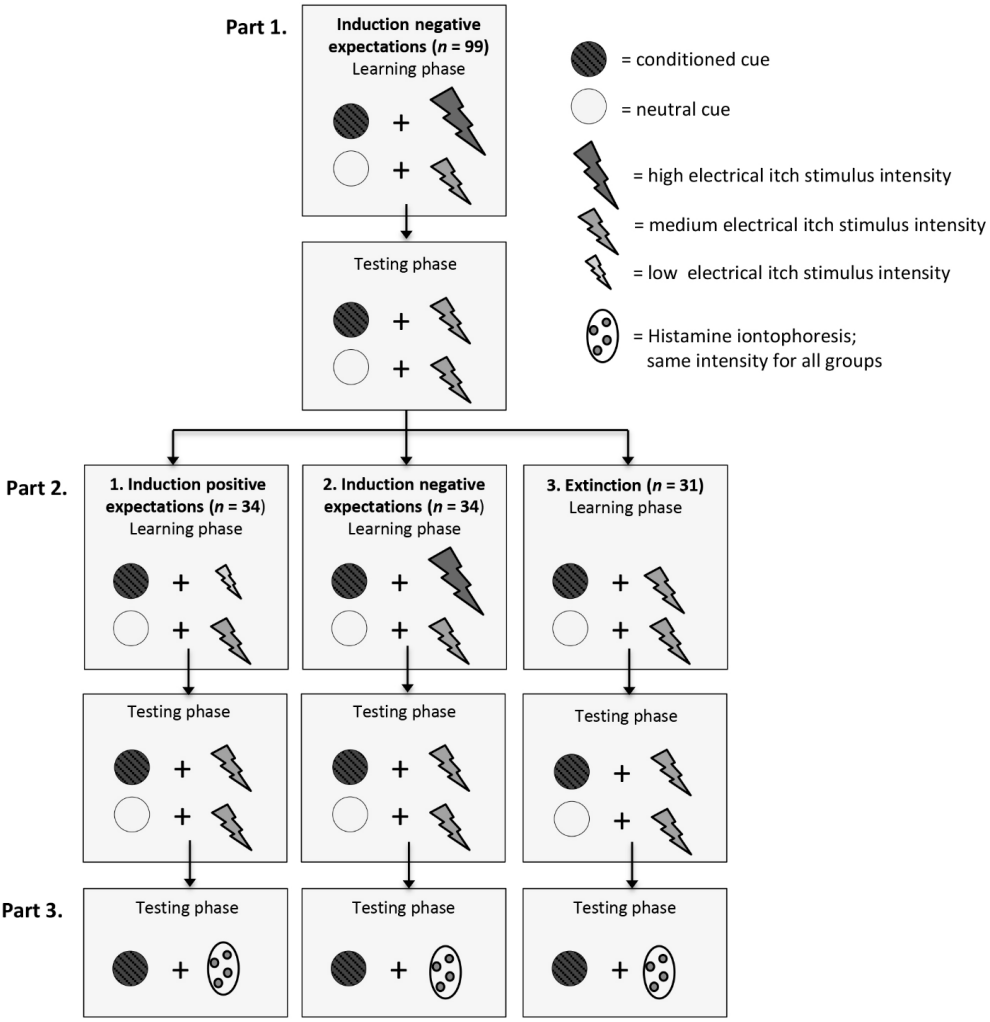

Fig 1. Experimental design. The study started with negative expectation induction: participants were told that the purple light (conditioned cue) indicated an increase in the itch stimulus, and that the yellow light (neutral cue) indicated no change in the itch stimulus. In accordance with the verbal suggestion, the purple and yellow lights were repeatedly paired with high and medium electrical itch stimulus intensities, respectively. Subsequently, participants were randomized over the three groups in which 1) positive expectations were induced; 2) continued negative expectations were induced; or 3) an extinction procedure was applied. In the learning phases verbal suggestion and conditioning procedures depended on the experimental group. In the testing phase the verbal suggestion corresponded to the verbal suggestion provided in the learning phase, while all participants received electrical itch stimuli of medium intensity. Next, generalization of reduced nocebo effects to histamine application was tested. The verbal suggestion corresponded to the verbal suggestion provided in part 2 and the purple light (conditioned cue) was displayed during the histamine application. The intensity of the histamine application was identical for all groups. Note that for half of the participants the conditioned cue was a purple light and the neutral cue a yellow light (like in this example); for the other half of the participants the conditioned cue was yellow and the neutral purple.

Materials

Itch induction

Electrical stimulation

Itch was induced by means of electrical stimulation using a constant current stimulator (Isolated Bipolar Constant Current Stimulator DS5, Digitimer, United Kingdom), and delivered to the inner side of the non-dominant wrist through two surface electrodes (for the detailed procedure see [15]). A third (sham) electrode was placed approximately 1 cm to the left from of the two active electrodes and attached to the back of the stimulator. Stimuli were applied at 50-Hz frequency with a pulse duration of 100 μs and at a continuously increasing current intensity (0.05 mA/s), up to a maximum current intensity of 5 mA. After each stimulus, participants verbally reported the level of itch, which they could express up to one decimal point, using a Numerical Rating Scale (NRS) ranging from 0.0 (no itch at all) to 10.0 (worst itch ever experienced). The NRS was attached below a computer screen in front of the participant.

Histamine iontophoresis

Histamine was applied by iontophoresis (Chattanooga Group, Hixson, TN, USA). A 0.3% diphosphate histamine solution was placed in an electrode (Chattanooga Ionto Ultra Electrode medium), which was placed on the dominant forearm (the forearm contralateral to the electrical itch stimulation), 2 cm distal to the lateral epicondyle of the humerus. The reference electrode was applied to the skin on the lateral side of the triceps brachial muscle. The histamine solution was delivered with a dose controller (Chattanooga ionto, Chattanooga Group, Hixson, TN, USA) for 2.5 minutes at a current level of 0.4 mA. The third (sham) electrode that was also applied during electrical stimulation, was placed approximately 1 cm to the left from of the two histamine electrodes and attached to the back of the electrical stimulator. Participants rated itch intensity on an NRS every 30 seconds during histamine application.

Questionnaires

Screening questionnaires on demographic variables, diseases, and physical complaints were used to check participants for inclusion and exclusion criteria. In addition, several individual self-report questionnaires were used to assess the following psychological characteristics: Optimism (The Revised Life Orientation Test; [34]) total scale $\alpha = 0.66$; Hope (The Dispositional Hope Scale; [35]) $\alpha = 0.81$; Worrying (The Penn State Worry Questionnaire; [36]) $\alpha = 0.91$; Neuroticisms and Extraversion (The Eysenck Personality Questionnaire; [37]

neuroticism scale α = 0.79, α extraversion scale = 0.85; Impulsivity (The Baratt Impulsiveness Scale; [38] α = 0.84; Self-efficacy (The General Self-Efficacy scale; [39]) α = 0.82; Negative affect (The Hospital Anxiety and Depression Scale; [40]) total scale α = 0.79; Future expectations (The Future Expectations questionnaire; [41]) positive scale α = 0.86, negative scale α 0.76; Positive and negative state affect (Positive and Negative Affect Schedule; [42]) positive affect scale α = 0.73. The negative affect scale data were not analyzed due to strong floor effects (53% of participants reported minimum score); State anxiety (short version of the State-Trait Anxiety Inventory, State version; [43]) α = 0.69; levels of itch, pain and fatigue (Numerical rating scale (NRS); [44], participants reported the experienced intensity of the sensations on a NRS ranging from 0.0 (no itch/ pain/ fatigue at all) to 10.0 (worst itch /pain/ fatigue ever experienced). Furthermore, exit questions regarding the intensity of the stimuli and purpose of the study were used. All questionnaires were administered in Dutch. With the exception of the exit questionnaires, which were filled out on paper, all questionnaires were completed using Qualtrics (Qualtrics, Provo, Utah, United States).

Procedure

The study was conducted at the Leiden University, Leiden, the Netherlands, from September 2014 to July 2015. Participants were recruited via an online recruitment system of Leiden University (Sona Systems, Tallinn, Estonia) and through flyers posted in the campus of the Leiden University, Leiden, the Netherlands. Participants were informed that the purpose of the study was to determine sensitivity to itch stimuli; the full purpose of the study was not revealed until after the experiment was finished. An online self-report questionnaire was used to screen participants for inclusion and exclusion criteria, and eligible participants were scheduled for an appointment. Next, participants filled out an additional online self-report questionnaires assessing personality traits.

All participants were asked to refrain from taking any medication, alcohol, and drugs for 24 hours before the test day, and from smoking cigarettes or drinking coffee, tea, cola, or energy drinks for two hours before testing. The experiment took place at a standard time (start at 11 am, duration ca. 5 hours and 30 minutes). First, all participants gave their written informed consent. Subsequently, baseline itch, pain, and fatigue were assessed using NRSs, and questionnaires on mood factors were administered. Before electrical stimulation, all participants held their hands in a warm water bath at about 32˚C for 3 minutes in order to

attain a comparable baseline wrist skin temperature among participants [15]. Next, the intensities of low, medium, and high stimuli were calibrated for each participant individually by gradually increasing the intensity of the electrical current with a ramping procedure (for the detailed procedure see [15]). The individually determined medium and high itch stimuli were used in part 1, and the low, medium and high itch stimuli were used in part 2 of this study.

In part 1, negative expectations regarding itch stimuli were induced in all participants by conditioning with verbal suggestion (part 1; induction of nocebo effect). Participants were told that they would receive a series of electrical itch stimuli with and without activation of a third electrode that influenced the itch intensity. This third electrode was actually never activated, since it was a sham electrode, serving as the 'placebo' in this experiment. Itch stimuli were accompanied by visual cues on a computer screen, i.e., purple and yellow colored circles. To control for effects of the colors, for half of the participants the conditioned cue was a purple circle and the neutral cue a yellow circle, and vice versa for the other half of the participants (an independent data manager generated an unpredictable random sequence via SPSS 23.0 for Windows; IBM SPSS Statistics, Chicago, Illinois, USA). Allocation to color was concealed by using sequentially numbered, opaque, envelopes that the experimenter opened just before the start of the learning phase in part 1 (1:1 allocation). The color was written on a folded sealed note. Participants were told: "A purple/ yellow light will signal the activation of the third electrode that induces an increase in the intensity of the itch stimulus, and the yellow/ purple light will indicate that the third electrode is turned off and will not change the intensity of the itch stimulus". Conditioning was achieved by surreptitiously increasing the intensity of the itch stimuli on the conditioned trials relative to the neutral trials.

In part 2, a computer generated randomization list (generated by the independent data manager using SPSS 23.0 for Windows; stratified by sex; with a 1:1:1 allocation) was used to assign participants randomly to one of the three groups (which differed only in the verbal suggestion and conditioning procedure). Just before the learning phase of part 2 started, the experimenter opened a second sealed note in the envelope in which the experimental condition was revealed. Participants were unaware of randomization or differences between groups during the experiment.

In the positive expectation induction group (induction of placebo effect; group 1), expectations of low and medium levels of itch were now raised in the participants: “A purple/ yellow light will signal the activation of the third electrode, which will now induce a decrease in the intensity of the itch stimulus, and the yellow/ purple light will indicate that the third electrode is turned off and will not change the intensity of the itch stimulus”. In accordance with the verbal suggestion, conditioning was now achieved by surreptitiously decreasing the intensity of the itch stimuli on the conditioned trials relative to the neutral trials. In the negative expectation induction group (induction of nocebo effect; group 2), exactly the same procedure was applied as in the first part of the experiment. In the extinction group (extinction; group 3), no verbal suggestion was provided, i.e., participants were not given any information about the colored cues or stimulus intensity and all stimuli were applied at medium intensity.

In line with previous studies of conditioning in relation to nocebo and placebo effects on pain e.g.,[19, 45] and with a previous study of our own [15], the experimental session comprised two phases: a learning phase and a testing phase. The learning phase consisted of 16 trials in total: 10 conditioned trials with supposed activation of the third (sham) electrode, and 6 neutral trials without activation of the third electrode. These trials were presented in a quasi-random order for each participant i.e., there were no more than two conditioned trials in a row. The testing phase consisted of 8 trials in total: 4 conditioned trials and 4 neutral trials, again in quasi-random order, all followed by itch stimuli of medium intensity. Conditioning took place only in the learning phase, but verbal suggestions were also repeated in the testing phase; the suggestions were the same as in the learning phase.

Each trial consisted of a single itch stimulus, which was accompanied by a visual colored cue (purple or yellow) on a computer screen. To announce the start of a trial, every itch stimulus was preceded by a flashing colored cue of one second on the computer screen. Between each electrical itch stimulus applied in the learning and testing phases, there was a 2-minute interval, in which filler tasks (“find the differences” tasks, “word search puzzles”, and “Sudoku puzzles”) were given to diminish possible influence on subsequent stimuli of itch evoked by previously applied stimuli. The interval could be extended to a maximum of 4 minutes if the level of itch after 2 minutes was ≥2.0 on an NRS.

In part 3, histamine iontophoresis followed, using the same verbal suggestion as in part 2 and displaying the same conditioned cue on the computer screen during administration of the histamine itch stimulus using distinct electrodes. Participants were told that histamine would be applied to the skin through a light electrical current and that the skin could get red and thicker, similar to a mosquito bite. Before histamine was applied, participants indicated baseline levels of itch, pain, and fatigue. Then, participants were told: "During the itch stimulus, again a colored cue will be displayed at the computer screen. This will either be or a purple light, or a yellow light". In the positive expectation induction group (induction of placebo effect; group 1), participants were told: "The purple/ yellow light will indicate a significant decrease in itch, and the yellow/ purple light will indicate that the itch remains unchanged". In the negative expectation induction group (induction of nocebo effect; group 2), participants were told: "The purple/ yellow light will indicate a significant increase in itch, and the yellow/ purple light will indicate that the itch remains unchanged". In the extinction group (extinction; group 3), no verbal suggestion was provided. In accordance with the electrical itch stimuli, the histamine itch stimulus was preceded by a flashing colored cue of one second on the computer screen. Even though participants were told that a purple or yellow light could be displayed, the color that was previously used for the conditioned trials (purple or yellow, depending on the randomization) was displayed. Moreover, the intensity of the histamine itch stimulus was, alike the testing phases in part 1 and 2 of the electrical stimulation equal for all groups.

Throughout the experiment participants were also videotaped in order to record scratching behavior and saliva was collected for DNA analyses (results will be reported elsewhere). The session was concluded with some questions regarding the perceived intensity of the itch stimuli and an open question to check whether participants were aware of the goal of the study.

During the test session, there were several standardized breaks. During the breaks, participants were provided a selected number of magazines to read, with neutral content (about nature and home decoration), and they were offered small snacks, Rooibos tea and water.

Since participants sat down during the whole experiment, in the break after testing phase 1 participants took a short 2-minute walk within the research area of the university to

stretch their legs, and used a home trainer in the lab at a slow pace for 5 minutes. There were no breaks between the learning and testing phases; the testing phases occurred immediately, without any signal.

Statistical analyses

All analyses were determined a priori in consultation with a statistician. The required sample size for the primary analysis was calculated with help from a statistician based on our previous study [15]. The analysis was approached in G* power 3.1 [46] as two two-tailed independent samples t-tests with Bonferroni correction. With an effect size d = 0.78, alpha α = 0.025 and a desired power of 0.80, this resulted in the largest required total sample size of 99 participants. In total 30 participants were excluded from data analysis on the basis of criteria determined in advance: for 1 participant, the experimenter provided a wrong combination of the conditioned cue with the verbal suggestion; 3 participants dropped out due to equipment failure; and 25 participants were excluded because they experienced little to no itch after repeated electrical itch induction (see also Fig 2. for more details on the number of participants at the different stages of the study). With the permission of the local ethical committee, it was decided to exclude all participants who rated the mean level of itch they experienced as < 1 itch on an NRS with regard to the itch stimuli associated with the neutral stimuli in the testing phase of part 2. These participants were replaced by randomly selected new participants. The statistical analyses were conducted over the participants who experienced ≥1 itch on an NRS (n = 99). However, sensitivity analyses were also carried out for all 124 participants who completed the study, of whom 25 had experienced < 1 itch on an NRS. All analyses were performed using SPSS 23.0 for Windows (IBM SPSS Statistics, Chicago, Illinois, USA). The nocebo effect was defined as the difference between the mean itch NRS scores associated with the four trials with the supposed activation of the third electrode (conditioned trials) and the four trials without the supposed activation of the third electrode (neutral trials) in the testing phase. A positive score indicated a nocebo effect.

Where the assumptions of the statistical tests (e.g., of normality) were violated, the data was transformed or non-parametric tests were used (if feasible). With regard to the nocebo effect in part 1 there was a problem with regard to normality of the data in the learning and testing phase. Although transformation did not result in normal distribution, parametric tests were reported, as non-parametric analyses obtained similar results.

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

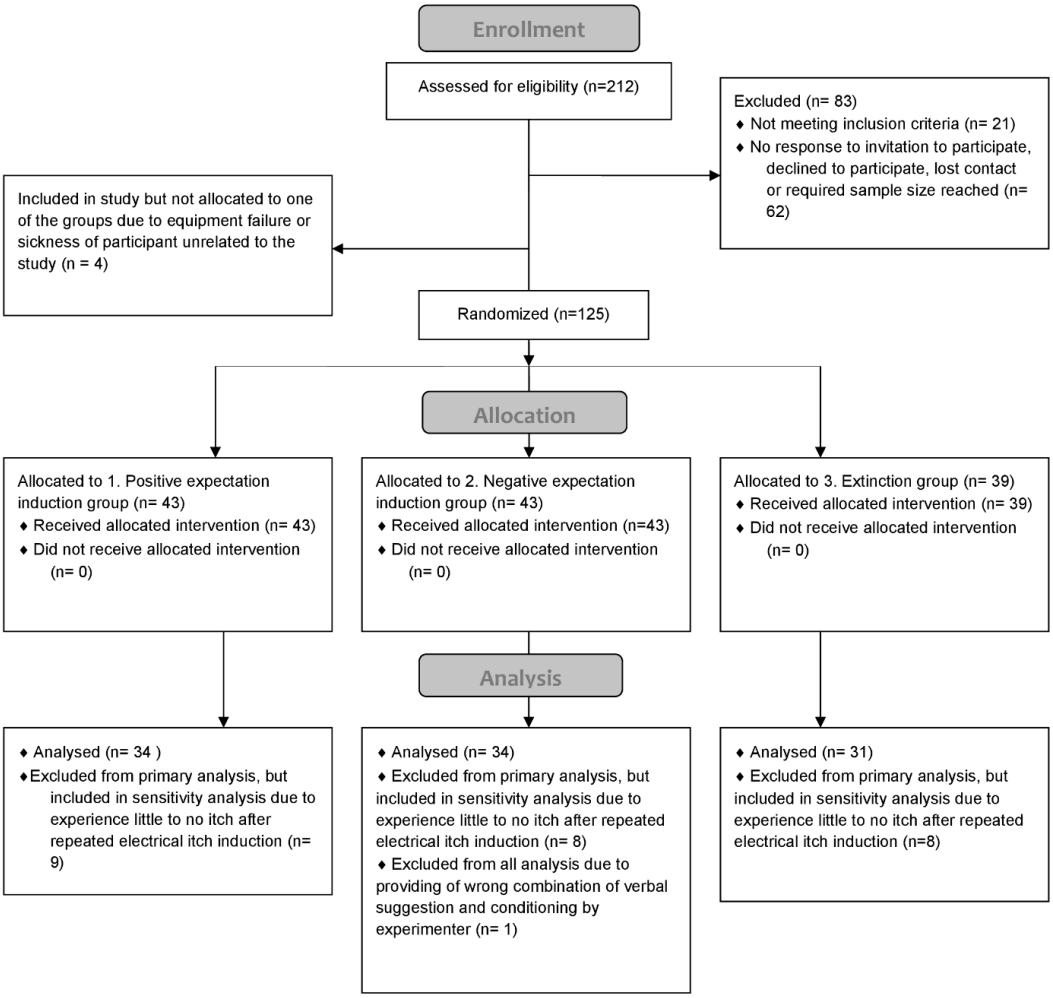

Fig 2. CONSORT flowchart.

Before conducting the main analysis, a paired samples t-test was performed to investigate whether there was a nocebo effect in the first part of the experiment by comparing the mean itch NRS score associated with the conditioned and neutral trials in the testing phase of part 1. As a manipulation check, the effectiveness of the negative expectation induction procedure

during the learning phase was also assessed in an exploratory manner. To this end, a paired samples t-test was again performed as described above, exploring the difference in itch NRS scores between the conditioned and neutral trials in the learning phase of part 1.

Next, a univariate analysis of variance (ANOVA) was performed with group as between-subject factor in the second part of the experiment, in order to test the main hypothesis, i.e., that the positive expectation induction group would display a significantly smaller nocebo effect than the control groups (negative expectation induction group or extinction group). Post hoc Dunnett tests were conducted to compare the positive expectation induction group with each of the control groups. As a manipulation check, the effectiveness of the expectation induction procedures during the learning phase was also assessed in an exploratory manner. Again, an Post hoc Dunnett tests were conducted to compare the positive expectation induction group with each of the control groups.

For exploratory purposes, Pearson correlation coefficients were calculated between the nocebo effects in the first as well as the second part (for each group separately) and questionnaire scores for psychological characteristics. For all analyses, the level of significance was set at $p<0.05$.

Results

In part 1, negative expectations were induced in all participants (induction nocebo effect). In part 2 (reversing nocebo effect), randomization of the participants across the three groups resulted in a total of 34 participants in the positive expectation induction group, 34 participants in the negative expectation induction group, and 31 participants in the extinction group. The characteristics of age, gender, use of hormonal contraceptives, baseline levels of itch, pain and fatigue on the test day, and baseline levels of itch, pain and fatigue before histamine iontophoresis for the randomized participants were similar in the groups (see Table 1).

Table 1. Participant characteristics

	1. Positive expectation induction	2. Negative expectation induction	3. Extinction
Age	20.4 ± 2.7	20.3 ± 2.7	19.9 ± 1.9
Male/female ratio %	26.5/73.5%	23.5/76.5%	19.4/80.6%
Hormonal contraceptives %	50.0%	50.0%	54.8%
Itch baseline test day NRS	0.6 ± 0.7	0.6 ± 0.7	0.6 ± 0.7
Pain baseline test day NRS	0.4 ± 0.9	0.4 ± 0.5	0.5 ± 0.7
Fatigue baseline test day NRS	2.4 ± 1.5	2.1 ± 1.5	2.1 ± 1.3
Itch baseline histamine NRS	1.0 ± 1.1	0.9 ± 1.1	0.6 ± 0.7
Pain baseline histamine NRS	0.7 ± 1.0	0.6 ± 0.6	0.6 ± 0.8
Fatigue baseline histamine NRS	3.6 ± 1.7	3.6 ± 1.3	3.8 ± 1.5

Characteristics of the participants in the positive expectation induction group (group 1; n=34), the negative expectation induction group (group 2; n=34), and the extinction group (group 3; n=31).

Induction of negative expectations (part 1)

Learning phase

As a manipulation check, the itch NRS scores evoked during the learning phase of part 1 were assessed. This involved the induction of negative expectations for all participants; both verbal suggestion and conditioning were applied. Table 2 displays the means (±SD) of the stimuli associated with the conditioned and neutral trials. A paired samples t-test revealed a significantly higher mean itch NRS score for the conditioned trials (M = 5.2, SD = 1.7) than for the neutral trials (M = 4.0, SD = 1.7) ($t(98) = 12.55$, $p<0.001$, $d = 1.26$). This result shows that the conditioning with verbal suggestion procedure was effective in inducing increased itch in the conditioned trials relative to the neutral trials.

Testing phase

In the testing phase of part 1, all participants received the same stimuli, which were applied at medium intensity. Table 2 displays the means (±SD) of the itch NRS scores evoked by the stimuli associated with the conditioned and neutral trials. A paired samples t-test revealed a significantly higher mean itch NRS score for the conditioned trials (M = 3.6, SD =

1.9) than for the neutral trials (M = 3.2, SD = 1.8) (t(98) = 4.85, p < .001, d = 0.49), indicating a significant nocebo effect in part1.

Table 2. Means (±*SD)* for itch NRS scores in the learning and testing phase in part 1 (induction of negative expectations)

	Itch NRS scores (*M* ± *SD*)		
	Conditioned trials	Neutral trials	Change in itch score
Learning phase	5.2 ± 1.7	4.0 ± 1.7	1.2 ± 0.9
Testing phase	3.6 ± 1.9	3.2 ± 1.9	0.4 ± 0.8

Means (*M*) and standard deviations (*SD*) of the numerical rating scale (NRS) scores for itch and change itch NRS score (itch NRS score in conditioned trials minus neutral trials) in the learning phase and testing phase for the induction of negative expectations in part 1 (*n=99*).

Reversing nocebo effect (part 2)

Learning phase

As a manipulation check, the itch NRS scores evoked during the learning phase of part 2 were assessed. Depending on the group, positive or negative expectations were induced by conditioning with verbal suggestion or an extinction procedure was applied. Table 3 displays the mean (±SD) itch NRS scores evoked by the stimuli associated with the conditioned and neutral trials during the learning phases for each group. When we tested whether the mean change itch NRS score (conditioned trials minus neutral trials) would be smaller in the positive expectation induction group in than in the control groups, univariate analysis of variance (ANOVA) revealed a significant group effect ($F(2,96) = 75.39$, $p<0.001$, $\eta_p^2 = 0.61$). Post hoc Dunnett tests indicated a significantly larger itch NRS change score between the conditioned and neutral trials, for the positive expectation induction group (M = -1.5, SD = 1.0) as compared to the negative expectation induction group (M = 1.2, SD = 0.8) (p = < 0.001) as well as the extinction group (M = 0.7, SD = 1.0)(p<0.001). This result reveals that the positive conditioning procedure was effective in inducing decreased itch in the conditioned trials relative to the neutral trials, in comparison with the control groups.

Testing phase

In the testing phase of part 2, all participants received the same stimuli, which were applied at medium intensity. Table 4 displays the mean (±SD) itch NRS scores evoked by the stimuli associated with the conditioned and neutral trials during the testing phase for each

Table 3. Means (*±SD)* for itch NRS scores in the learning phase for the different groups in part 2

	Itch NRS scores (*M ± SD*)		
	Conditioned trials	Neutral trials	Change in itch score
Group 1 *- Positive expectation induction*	1.9 ± 1.5	3.3 ± 1.0	-1.5 ± 1.0
Group 2 *– Negative expectation induction*	4.2 ± 1.5	3.0 ± 1.5	1.2 ± 0.8
Group 3 *– Extinction*	3.8 ± 1.6	3.1 ± 1.6	0.7 ± 1.0

Means (*M*) and standard deviations (*SD*) of the numerical rating scale (NRS) scores for itch and for the change itch score (itch NRS score conditioned trials minus neutral trials) in the *positive expectation induction group* (group 1; *n*=34), the *negative expectation induction group* (group 2; *n*=34) and the *extinction group* (group 3; *n*=31) in the learning phase of part 2.

Table 4. Means (*±SD)* for itch NRS scores in the testing phase for the different groups in part 2

	Itch NRS scores (*M ± SD*)		
	Conditioned trials	Neutral trials	Change in itch score
Group 1 *- Positive expectation induction*	2.4 ± 1.5	2.9 ± 1.5	-0.4 ± 1.0
Group 2 *– negative expectation induction*	3.4 ± 1.7	2.9 ± 1.9	0.5 ± 0.8
Group 3 *– Extinction*	2.9 ± 1.9	2.6 ± 1.9	0.3 ± 0.9

Means (M) and standard deviations (SD) of the numerical rating scale (NRS) scores for itch and for the change in itch score (itch NRS score conditioned trials minus neutral trials) in the positive expectation induction group (group 1; n=34), the negative expectation induction group (group 2; n=34) and the extinction group (group 3; n=31) in the testing phase of part 2.

group. The mean nocebo effect for each group is shown in Fig 3. When we tested the main hypothesis that the nocebo effect would be smaller in the positive expectation induction group than in the control groups, univariate ANOVA showed a significant difference in the magnitude of the nocebo effect in the various groups ($F(2,96) = 9.93$, $p<0.001$, $\eta_p^2 = 0.17$). Post hoc Dunnett tests comparing the experimental group with the control groups indicated a significantly smaller nocebo effect in the positive expectation induction group (M = -0.4, SD =

1.0) than in the negative expectation induction group (M = 0.5, SD = 0.8) (p<0.001) and the extinction group (M = 0.3, SD = 0.9) (p = 0.003) (See Fig 3.).

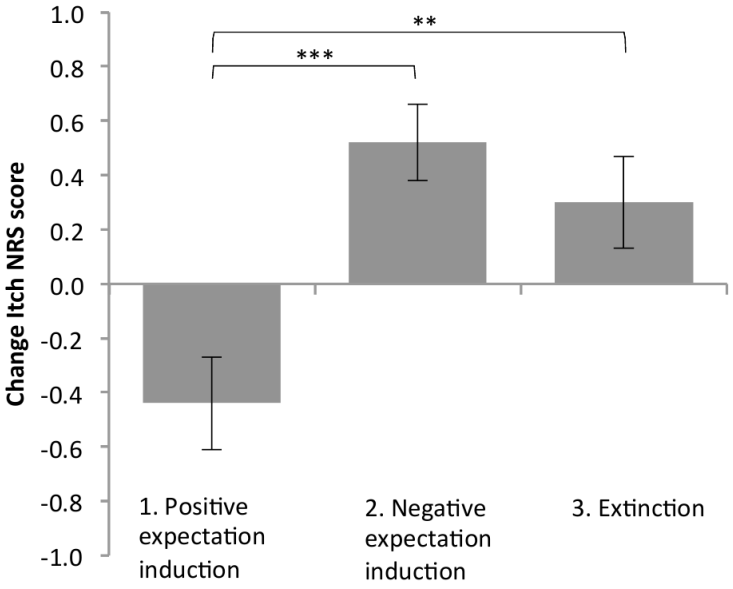

Fig 3. Nocebo effect. Means and standard error of the mean (error bars) of the numerical rating scale (NRS) itch scores for the nocebo effect (change in itch NRS score between the four conditioned and four neutral trials) of the different groups in the testing phase of part 2 (higher value indicates higher nocebo effect). The asterisks show the level of significance related to the post hoc Dunnett comparison (***p<0.001; **p<0.01).

Generalization of nocebo effects to histamine iontophoresis

When we explored whether the reduced nocebo effect generalized to the histamine stimulus, an ANOVA showed a significant main effect for the groups with regard to the mean itch NRS score during histamine application ($F(2,96) = 5.293$, $p<0.01$, $\eta_p^2 = 0.10$). Post hoc Dunnett tests comparing the experimental group with the control groups indicated significantly lower itch NRS scores in the positive expectation induction group (M = 5.7, SD = 0.3) than in the negative expectation induction group (M = 6.8, SD = 0.3) (p<0.01) and marginally significant itch NRS scores in the positive expectation induction group than in the extinction group (M = 6.5, SD = 0.3) (p = 0.058).

Psychological characteristics

When we calculated correlation coefficients between the nocebo effect in part 1 (induction negative expectations) and psychological characteristics, no significant correlations

were found. Similarly, when we calculated correlations coefficients between the psychological characteristics and the nocebo effect in part 2 for each group separately (reversing nocebo effect), no significant correlations were found.

Sensitivity analyses

Sensitivity analyses were conducted regarding the main analysis to assess the influence of excluding the data of 25 participants who experienced little to no itch after repeated electrical itch induction (< 1 itch on an NRS, see methods, statistical analyses). When all 124 participants who completed the study were included, similar effects were found. More specifically, when we investigated whether there was a significant nocebo effect in the testing phase of part 1, a paired samples t-test revealed a significantly higher mean itch NRS score for the conditioned trials (M = 3.2, SD = 2.0) than for the neutral trials (M = 2.8, SD = 1.9) ($t(123) = 5.45$, $p < .001$, $d = 0.96$). This indicates that the nocebo effect in part 1 was significant. When we tested the main hypothesis that, if all 124 participants were included, the nocebo effect in part 2 would be smaller in the positive expectation induction group than in the control groups, univariate ANOVA showed a significant difference in the magnitude of the nocebo effect in the various groups ($F(2, 121) = 12.23$, $p < 0.001$, $\eta_p^2 = 0.17$). Post hoc Dunnett tests comparing the experimental group with the control groups indicated a significantly smaller nocebo effect in the positive expectation induction group (n = 43) (M = -0.4, SD = 0.9) than the negative expectation induction group (n = 42) (M = 0.5, SD = 0.8) ($p < 0.001$) and in the extinction group (n = 39) (M = 0.3, SD = 0.9) ($p < 0.01$).

Discussion

The present study demonstrates, for the first time, that nocebo effects induced by conditioning with verbal suggestion can be minimized and even reversed by positive expectation induction by means of counterconditioning with verbal suggestion. Participants who received the positive expectation induction experienced significantly less itch than participants in the control groups, who received either continued negative expectation induction or an extinction procedure. Moreover, these results generalized to a second itch stimulus. These results demonstrate that a single session of counterconditioning with verbal suggestion is sufficient to reverse previously induced nocebo effects and elicit placebo effects.

In line with our previous studies on nocebo effects on itch [14, 15], exposing the participants to negative expectations (i.e., expectations for high levels of itch) regarding the conditioned trials, resulted in significantly higher levels of itch in response to the conditioned trials than to the neutral trials; this indicates that the nocebo induction was successful. This finding replicates results from a previous study [15], in which we demonstrated that nocebo effects on itch can be induced by the combination of conditioning and verbal suggestion. This is in accordance with studies on other physical symptoms like pain [19–21]. Furthermore, the result is consistent with previous studies that demonstrate that verbal suggestion alone can induce nocebo effects, or nocebo-like effects, on itch [14, 16, 47, 48]. The current study not only replicates the finding that nocebo effects on itch can be induced by conditioning and verbal suggestion [15], but also extends this by demonstrating that nocebo effects can be reversed. To the best of our knowledge, this is the first time that this has been investigated.

Positive expectation induction in the conditioned trials resulted in a significantly smaller nocebo effect than in the control groups, in which negative expectations were induced or an extinction procedure was applied. Moreover, the nocebo effect after positive expectation induction even demonstrated a significant placebo effect. Additional support for these findings was found in the learning phase, in which there was a similar pattern of changes in itch scores in response to conditioned and neutral trials. This finding extends results of a recent study on nocebo-like effects induced by verbal suggestions, which provided some initial indications that positively framed information regarding the health effects of wind turbine sound can dilute or even reverse the effects of negative expectations [22]. The successful reversal of the nocebo effect on itch by means of a counterconditioning procedure is consistent with a large body of research that shows that counterconditioning is an effective way of changing learned behavior in, for example, fear and evaluative conditioning paradigms [23–25, 32]. Furthermore, the finding that counterconditioning by inducing positive expectations was more effective than an extinction procedure in reversing the nocebo effect is also in accordance with conditioning studies that indicate that counterconditioning might be more effective than extinction in changing conditioned effects [23–25, 32].

In the current study, the extinction procedure did not significantly reduce nocebo effects. This is in line with previous studies on pain showing that nocebo effects eventually decrease but often do not fully eliminate the learned behavior, especially when a high number

of conditioning trials is used [19, 45, 49]. Since in these studies and the current one the number of extinction trials was limited to a maximum of 10, it is currently unknown whether nocebo effects might be extinguished after more extinction trials or after several days. Similarly, evaluative conditioned effects seem less sensitive to extinction than conditioned fear responses, which often do become extinct after extinction trials [19, 45, 49]. In evaluative conditioning this is explained by the fact that the nonoccurrence of the US disconfirms the predictive value of the CS, but still evokes the representation of the US with the accompanying evaluation [31, 32]. More research is needed to establish whether similar processes could play a role in nocebo effects.

We found indications that the reduced nocebo effect generalized to a second, different itch stimulus i.e., histamine iontophoresis. The demonstration of possible generalization to other stimuli lends weight to the effectiveness of the counterconditioning with verbal suggestion procedure for the reduction of nocebo effects. However, future research should investigate whether this generalization is still effective without repeating verbal suggestions, as it was applied in our study before the histamine application. Moreover, this finding supports the external validity of the counterconditioning with verbal suggestion paradigm employed in this experiment. Therefore, also for other physical sensations like pain, it would be highly relevant to investigate the reversibility of nocebo effects, to get insight into expectancy learning in reversing nocebo effects across different sensations.

In the present study we did not find any significant correlations with the psychological characteristics examined. Previous studies regarding nocebo effects on itch have found indications for a role of psychological characteristics in relation to negative outcome expectancies, like worrying or negative affect, however research is extremely scarce [50]. Moreover, in a recent study by our research group, indications were found that one's cognitive schemas regarding specificity and valence of memories and expectations regarding itch are related to placebo responding on itch, i.e., participants who were more specific in their memories regarding itch and who had less negative itch-related expectations for the future were more likely to be placebo itch responders [33]. Future research should further investigate the determinants of (reversing) nocebo responses, like individual differences in psychological characteristics in relation to negative outcome expectancies and cognitive schemas regarding memories and expectations.

Several implications for future research and clinical practice should be considered. First, the counterconditioning with verbal suggestion paradigm could possibly be applied to other experimental models of itch, like mechanical itch stimuli, to study different itch pathways that are relevant for different types of pruritus that can be seen in clinical practice [51, 52]. Second, it remains to be established whether these findings in healthy participants can be generalized to patients in a clinical setting. Two studies regarding contagious itch suggest that patients with chronic itch complaints might respond more strongly to visual or audiovisual itch cues than healthy controls [13, 53]. Additionally, several neuroimaging studies demonstrate differences in brain activation when itch is experimentally induced in patients versus in healthy controls [54, 55], emphasizing the need to study the placebo and nocebo effects on itch separately for healthy controls and patients. Furthermore, future research should investigate how experimental conditioning paradigms can be used in clinical practice. For example pharmacotherapeutic conditioning designs regarding itch medication, aimed at reducing the dose of medication could be examined. For example, a related format has been used in a study in patients with allergic rhinitis, in which an H1 receptor antagonist was conditioned with a novel-tasting drink, and in the testing phase replaced by a placebo with the drink. Patients reported less subjective symptoms and showed a reduced skin response to the skin prick test when administering the drink along with a placebo pill [6]. Future research could set up a similar design with reducing the dosage of itch medication to diminish possible side effects while the therapeutic benefits of the medication are preserved [56]. Minimizing possible nocebo effects could be an important ingredient of individually tailored care interventions for chronic somatic conditions [11, 57, 58]. This may be particularly important for patients with negative expectations regarding the given treatment, for example for patients with negative treatment experiences or certain personality characteristics related to negative treatment outcomes (e.g., worrying), or for patients who are excessively afraid of side effects [1, 50, 59, 60].

A possible limitation of this study is that reversal of the nocebo effect was tested in a single session. It would be highly relevant to test whether the reversed nocebo effect, i.e., placebo effect, remains on subsequent days, whether it extinguishes, or whether the nocebo effect recurs. Furthermore, we did not investigate the influence of the filler tasks provided between the electrical itch stimuli. Although we selected different tasks that were in general

not too challenging and as neutral as possible, we cannot exclude a possible influence on for example mood, which can vary between individual participants. In addition, we did not assess participants' expectations over the course of the study, so we cannot exclude the possibility that factors other than expectancy learning might be responsible for the effects found in this study. Moreover, assessing participants' expectations in future studies would provide valuable data on how the induction of negative and subsequently of positive expectations affects patients' expectations overall, and on the extent to which these expectations mediate nocebo effects.

In conclusion, this study demonstrates that nocebo effects can be effectively minimized by positive expectation induction and can even turn into placebo effects. Moreover, counterconditioning of nocebo effects regarding one stimulus can possibly generalize to another similar stimulus. Whereas more research is needed, the results of the current study show first indications that learning via counterconditioning and verbal suggestion may represent a promising strategy for diminishing nocebo responses.

Supporting information

S1 Checklist. CONSORT 2010 checklist of information to include when reporting a randomised trial. (DOCX)

S1 Protocol. Research Protocol.
(PDF)

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References

1. Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. Psychosom Med. 2011; 73(7):598–603. Epub 2011/08/25. https://doi.org/10.1097/PSY.0b013e3182294a50 PMID: 21862825; PubMed Central PMCID: PMC3167012.
2. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. JAMA. 2002; 287(5):622–7. PMID: 11829702.
3. Faasse K, Petrie KJ. The nocebo effect: patient expectations and medication side effects. Postgrad Med J. 2013; 89(1055):540–6. https://doi.org/10.1136/postgradmedj-2012-131730 PMID: 23842213.
4. Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med. 2011; 3(70):70ra14. https://doi.org/10.1126/scitranslmed.3001244 PMID: 21325618.
5. Benedetti F. Placebo effects: Oxford University Press, USA; 2014.
6. Goebel MU, Meykadeh N, Kou W, Schedlowski M, Hengge UR. Behavioral conditioning of antihistamine effects in patients with allergic rhinitis. Psychotherapy and psychosomatics. 2008; 77(4):227–34. https://doi.org/10.1159/000126074 PMID: 18418029.
7. Tekampe J., van Middendorp H., Meeuwis S.H., van Leusden J.W.R., Pacheco-López G., Hermus A.R. M.M., and Evers A.W.M. Conditioning immune and endocrine parameters in humans: A systematic review. Under review in Psychother Psychosom. https://doi.org/10.1159/000449470 PMID: 28183096
8. Verhoeven EW, de Klerk S, Kraaimaat FW, van de Kerkhof PC, de Jong EM, Evers AW. Biopsychosocial mechanisms of chronic itch in patients with skin diseases: a review. Acta Derm Venereol. 2008; 88 (3):211–8. Epub 2008/05/16. https://doi.org/10.2340/00015555-0452 PMID: 18480917.
9. Evers AW, Duller P, van de Kerkhof PC, van der Valk PG, de Jong EM, Gerritsen MJ, et al. The Impact of Chronic Skin Disease on Daily Life (ISDL): a generic and dermatology-specific health instrument. Br J Dermatol. 2008; 158(1):101–8. Epub 2007/11/15. https://doi.org/10.1111/j.1365-2133.2007.08296.x PMID: 17999699.
10. Tey HL, Wallengren J, Yosipovitch G. Psychosomatic factors in pruritus. Clin Dermatol. 2013; 31 (1):31–40. https://doi.org/10.1016/j.clindermatol.2011.11.004 PMID: 23245971; PubMed Central PMCID: PMC3690364.
11. Evers AW, Gieler U, Hasenbring MI, van Middendorp H. Incorporating biopsychosocial characteristics into personalized healthcare: a clinical approach. Psychotherapy and psychosomatics. 2014; 83 (3):148–57. https://doi.org/10.1159/000358309 PMID: 24732828.
12. Holle H, Warne K, Seth AK, Critchley HD, Ward J. Neural basis of contagious itch and why some people are more prone to it. Proc Natl Acad Sci U S A. 2012; 109(48):19816–21. Epub 2012/11/15. https://doi.org/10.1073/pnas.1216160109 PMID: 23150550; PubMed Central PMCID: PMC3511754.
13. Papoiu AD, Wang H, Coghill RC, Chan YH, Yosipovitch G. Contagious itch in humans: a study of visual 'transmission' of itch in atopic dermatitis and healthy subjects. Br J Dermatol. 2011; 164(6):1299–303. Epub 2011/03/18. https://doi.org/10.1111/j.1365-2133.2011.10318.x PMID: 21410682; PubMed Central PMCID: PMC3110738.
14. van Laarhoven AI, Vogelaar ML, Wilder-Smith OH, van Riel PL, van de Kerkhof PC, Kraaimaat FW, et al. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain. 2011; 152 (7):1486–94. Epub 2011/03/01. https://doi.org/10.1016/j.pain.2011.01.043 PMID: 21353388.
15. Bartels DJ, van Laarhoven AI, Haverkamp EA, Wilder-Smith OH, Donders AR, van Middendorp H, et al. Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. PLoS One. 2014; 9 (3):e91727. https://doi.org/10.1371/journal.pone.0091727 PMID: 24646924; PubMed Central PMCID: PMC3960153.
16. Napadow V, Li A, Loggia ML, Kim J, Mawla I, Desbordes G, et al. The imagined itch: brain circuitry supporting nocebo-induced itch in atopic dermatitis patients. Allergy. 2015; 70(11):1485–92. https://doi.org/10.1111/all.12727 PMID: 26280659; PubMed Central PMCID: PMC4609272.
17. van Laarhoven AI, van der Sman-Mauriks IM, Donders AR, Pronk MC, van de Kerkhof PC, Evers AW. Placebo Effects on Itch: A Meta-Analysis of Clinical Trials of Patients with Dermatological Conditions. J Invest Dermatol. 2015; 135(5):1234–43. https://doi.org/10.1038/jid.2014.522 PMID: 25609025.

18. Benedetti F. Mechanisms of placebo and placebo-related effects across diseases. Annu Rev Pharmacol. 2008; 48:33–60. https://doi.org/10.1146/annurev.pharmtox.48.113006.094711 ISI:000253396900002. PMID: 17666008

19. Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. Pain. 2008; 136 (1–2):211–8. https://doi.org/10.1016/j.pain.2008.02.006 ISI:000255821900025. PMID: 18372113

20. Carlino E, Torta DM, Piedimonte A, Frisaldi E, Vighetti S, Benedetti F. Role of explicit verbal information in conditioned analgesia. European journal of pain. 2015; 19(4):546–53. https://doi.org/10.1002/ejp.579 PMID: 25161110.

21. Quinn VF, Colagiuri B. Sources of Placebo-Induced Relief From Nausea: The Role of Instruction and Conditioning. Psychosom Med. 2016; 78(3):365–72. https://doi.org/10.1097/PSY.0000000000000265 PMID: 26588822.

22. Crichton F, Petrie KJ. Accentuate the positive: Counteracting psychogenic responses to media health messages in the age of the Internet. Journal of psychosomatic research. 2015; 79(3):185–9. https://doi.org/10.1016/j.jpsychores.2015.04.014 PMID: 25963037.

23. Gast A, De Houwer J. The influence of extinction and counterconditioning instructions on evaluative conditioning effects. Learning and Motivation. 2013; 44(4):312–25.

24. De Houwer J. A conceptual and theoretical analysis of evaluative conditioning. Span J Psychol. 2007; 10(2):230–41. PMID: 17992949.

25. Kerkhof I, Vansteenwegen D, Baeyens F, Hermans D. Counterconditioning. Experimental psychology. 2015.

26. Van Gucht D, Baeyens F, Vansteenwegen D, Hermans D, Beckers T. Counterconditioning reduces cue-induced craving and actual cue-elicited consumption. Emotion. 2010; 10(5):688–95. https://doi.org/10.1037/a0019463 PMID: 21038951.

27. Kanfer FH, Phillips JS. Learning foundations of behavior therapy. New York,: Wiley; 1970. xi, 642 p. p.

28. Baeyens F, Eelen P, Van Den Bergh O, Crombez G. Acquired affective-evaluative value: conservative but not unchangeable. Behav Res Ther. 1989; 27(3):279–87. PMID: 2730509.

29. Meulders A, Karsdorp PA, Claes N, Vlaeyen JWS. Comparing Counterconditioning and Extinction as Methods to Reduce Fear of Movement-Related Pain. Journal of Pain. 2015; 16(12):1353–65. https://doi.org/10.1016/j.jpain.2015.09.007 WOS:000366443000013. PMID: 26434783

30. Bandura A. Principles of behavior modification. New York,: Holt; 1969. ix, 677 p. p.

31. Raes AK, De Raedt R. The effect of counterconditioning on evaluative responses and harm expectancy in a fear conditioning paradigm. Behav Ther. 2012; 43(4):757–67. https://doi.org/10.1016/j.beth.2012.03.012 PMID: 23046778.

32. Kerkhof I, Vansteenwegen D, Baeyens F, Hermans D. Counterconditioning: an effective technique for changing conditioned preferences. Exp Psychol. 2011; 58(1):31–8. https://doi.org/10.1027/1618-3169/a000063 PMID: 20382627.

33. Bartels DJ, van Laarhoven AI, Heijmans N, Hermans D, Debeer E, van de Kerkhof PC, et al. Cognitive Schemas in Placebo and Nocebo Responding: Role of Autobiographical Memories and Expectations. Clinical therapeutics. 2017; 39(3):502–12 e1. https://doi.org/10.1016/j.clinthera.2017.02.004 PMID: 28341522.

34. Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, selfmastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol. 1994; 67 (6):1063–78. Epub 1994/12/01. PMID: 7815302.

35. Snyder CR, Harris C, Anderson JR, Holleran SA, Irving LM, Sigmon ST, et al. The will and the ways: Development and validation of an individual-differences measure of hope. J Pers Soc Psychol. 1991; 60(4):570–85. PMID: 2037968

36. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State worry questionnaire. Behaviour research and therapy. 1990; 28(6):487–95. PMID: 2076086

37. Eysenck HJ, Eysenck SBG. EPQ (Eysenck Personality Questionnaire): Educational and Industrial Testing Service; 1975.

38. Stanford MS, Mathias CW, Dougherty DM, Lake SL, Anderson NE, Patton JH. Fifty years of the Barratt Impulsiveness Scale: An update and review. Pers Indiv Differ. 2009; 47(5):385–95. https://doi.org/10.1016/j.paid.2009.04.008 WOS:000267842200001.

39. Leganger A, Kraft P, Roysamb E. Perceived self-efficacy in health behaviour research: Conceptualisation, measurement and correlates. Psychology & Health. 2000; 15(1):51–69. https://doi.org/10.1080/08870440008400288 WOS:000086000900005.

40. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica. 1983; 67(6):361–70. PMID: 6880820

41. Hanssen MM, Peters ML, Vlaeyen JW, Meevissen YM, Vancleef LM. Optimism lowers pain: evidence of the causal status and underlying mechanisms. Pain. 2013; 154(1):53–8. https://doi.org/10.1016/j.pain.2012.08.006 PMID: 23084002.

42. Kercher K. Assessing Subjective Well-Being in the Old-Old—the Panas as a Measure of Orthogonal Dimensions of Positive and Negative Affect. Res Aging. 1992; 14(2):131–68. https://doi.org/10.1177/0164027592142001 WOS:A1992HY20100001.

43. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). The British journal of clinical psychology / the British Psychological Society. 1992; 31 (Pt 3):301–6. PMID: 1393159.

44. Hartrick CT, Kovan JP, Shapiro S. The numeric rating scale for clinical pain measurement: a ratio measure? Pain Pract. 2003; 3(4):310–6. https://doi.org/10.1111/j.1530-7085.2003.03034.x PMID: 17166126.

45. Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F. How the number of learning trials affects placebo and nocebo responses. Pain. 2010; 151(2):430–9. https://doi.org/10.1016/j.pain.2010.08.007 ISI:000282826100027. PMID: 20817355

46. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior research methods. 2007; 39(2):175–91. https://doi.org/10.3758/Bf03193146 WOS:000248501300003. PMID: 17695343

47. Darragh M, Chang JW, Booth RJ, Consedine NS. The placebo effect in inflammatory skin reactions: The influence of verbal suggestion on itch and weal size. Journal of psychosomatic research. 2015; 78(5):489–94. https://doi.org/10.1016/j.jpsychores.2015.01.011 PMID: 25649275.

48. Scholz O, Hermanns N. Illness behavior and cognitions influence the perception of itching of patients suffering from atopic dermatitis. Z Klin Psychol. 1994; 23:127–35.

49. Colagiuri B, Quinn VF, Colloca L. Nocebo hyperalgesia, partial reinforcement, and extinction. J Pain. 2015. https://doi.org/10.1016/j.jpain.2015.06.012 PMID: 26168876.

50. Bartels DJ, van Laarhoven AI, van de Kerkhof PC, Evers AW. Placebo and nocebo effects on itch: effects, mechanisms, and predictors. European journal of pain. 2016; 20(1):8–13. https://doi.org/10.1002/ejp.750 PMID: 26417885.

51. Andersen HH, Elberling J, Arendt-Nielsen L. Human surrogate models of histaminergic and non-histaminergic itch. Acta Derm Venereol. 2015; 95(7):771–7. https://doi.org/10.2340/00015555-2146 PMID: 26015312.

52. Papoiu AD, Tey HL, Coghill RC, Wang H, Yosipovitch G. Cowhage-induced itch as an experimental model for pruritus. A comparative study with histamine-induced itch. PLoS One. 2011; 6(3):e17786. Epub 2011/03/23. https://doi.org/10.1371/journal.pone.0017786 PMID: 21423808; PubMed Central PMCID: PMC3056722.

53. Schut C, Bosbach S, Gieler U, Kupfer J. Personality traits, depression and itch in patients with atopic dermatitis in an experimental setting: a regression analysis. Acta Derm Venereol. 2014; 94(1):20–5. https://doi.org/10.2340/00015555-1634 PMID: 23756579.

54. Ishiuji Y, Coghill RC, Patel TS, Oshiro Y, Kraft RA, Yosipovitch G. Distinct patterns of brain activity evoked by histamine-induced itch reveal an association with itch intensity and disease severity in atopic dermatitis. Br J Dermatol. 2009; 161(5):1072–80. https://doi.org/10.1111/j.1365-2133.2009.09308.x PMID: 19663870; PubMed Central PMCID: PMC2784001.

55. Schneider G, Stander S, Burgmer M, Driesch G, Heuft G, Weckesser M. Significant differences in central imaging of histamine-induced itch between atopic dermatitis and healthy subjects. European journal of pain. 2008; 12(7):834–41. https://doi.org/10.1016/j.ejpain.2007.12.003 PMID: 18203636.

56. Colloca L, Miller FG. Harnessing the placebo effect: the need for translational research. Philos T R Soc B. 2011; 366(1572):1922–30. https://doi.org/10.1098/rstb.2010.0399 WOS:000290617600017. PMID: 21576150

57. Misery L, Carre JL. Placebo and nocebo effects as major components of the treatment of itch. Exp Dermatol. 2017; 26(1):24–5. https://doi.org/10.1111/exd.13232 PMID: 27706855.

58. Evers AW. Using the placebo effect: how expectations and learned immune function can optimize dermatological treatments. Exp Dermatol. 2017; 26(1):18–21. https://doi.org/10.1111/exd.13158 PMID: 27489170.

59. Hofmann M, Wrobel N, Kessner S, Bingel U. Minimizing Carry-Over Effects After Treatment Failure and Maximizing Therapeutic Outcome Can Changing the Route of Administration Mitigate the Influence of Treatment History? Z Psychol. 2014; 222(3):171–8. https://doi.org/10.1027/2151-2604/a000180 WOS:000341284600009.

60. Kessner S, Wiech K, Forkmann K, Ploner M, Bingel U. The Effect of Treatment History on Therapeutic Outcome: An Experimental Approach. Jama Intern Med. 2013; 173(15):1468–9. https://doi.org/10.1001/jamainternmed.2013.6705 WOS:000324440400020. PMID: 23780284

CHAPTER 5

NOCEBO EFFECTS AND SCRATCHING BEHAVIOUR ON ITCH

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Abstract

Nocebo effects, i.e. reduced treatment effects due to patients' negative expectations, play a role in itch. Recent studies have shown that nocebo effects can be induced experimentally on itch and also be minimized and even turned into the opposite direction, i.e. placebo effects. It is not known whether these effects generalize to itch-associated scratching behaviour. The aim of this study was to determine whether induction and reversal of nocebo effects on itch evoked by electrical and histamine stimuli generalized to scratching. Ninety-seven healthy participants were included in the study. The manipulation was successful, as during the nocebo learning phase, increased scratching responses were found for higher intensity compared with lower intensity itch stimuli. During the testing phase of induction or reversal of the nocebo effects, however, no significant nocebo effects or reversed nocebo effects, were found in scratching. Thus, no straightforward generalization of nocebo effects from itch to scratching was found in this laboratory setting. Further investigation into possible generalization is needed in different settings and in patients with chronic itch.

Introduction

Itch and scratching are common symptoms in skin conditions such as psoriasis and atopic dermatitis, and can cause significant impairment for patients (1). Scratching may have an important role in the maintenance and exacerbation of skin conditions due to a vicious itch-scratch circle (2, 3). Effects of pharmacological treatments are relatively limited and these treatments often have side-effects (4). Treatment effectiveness may be improved by optimizing placebo effects, while minimizing nocebo effects (5, 6).

Placebo and nocebo effects are positive and negative treatment effects, unrelated to the treatment mechanism, which are induced by patients' expectations of improvement or worsening, respectively (7–9). Placebo and nocebo effects are known to contribute to various conditions and symptoms, and have been investigated mainly with regard to pain (7). Recent studies have demonstrated that placebo effects can reduce levels of itch in healthy participants as well as in patients with clinical itch due to chronic conditions (5, 6, 10, 11). Moreover, nocebo effects, which may play an even more important role in clinical practice (8, 12), can amplify itch, and these nocebo effects on itch can also be minimized and even turned into the opposite direction, i.e. a placebo effect (13). Overall, the combination of enhancing placebo effects on itch and reversing nocebo effects seems to be a promising target to further optimize treatment effects for itch. In addition, there are indications that placebo and nocebo effects on a specific symptom can generalize to other modalities or domains (14–19). Thus, nocebo and placebo effects associated with itch treatments may also generalize to the behavioural domain, by which patients' scratching behaviour (14, 15) may be influenced in a negative or positive direction, respectively.

Studies on contagious itch provide some evidence that nocebo-like effects on itch are also seen on scratching behaviour. For example, when participants watched videos of people scratching compared with control videos, they not only reported higher ratings of overall itch, but also scratched more frequently, with the largest effects for patients with chronic itch (16). However, it is not known whether induced nocebo effects on itch also generalize to scratching behaviour.

The aim of this experimental study was to investigate, for the first time, whether induced nocebo effects on itch (electrically induced) generalize to scratching behaviour in healthy

participants. As described previously in our article focusing on the levels of itch experienced within the same experiment (13), participants first learned negative expectations about electrical itch stimuli by coupling (through conditioning and verbal suggestions) a certain cue with increased intensities of itch. Next, participants were randomized to either the experimental group in which the cue was coupled with lowered itch intensities (positive expectation induction) or one of the control groups in which either negative expectation induction with the increased intensities of itch continued, or no expectations were induced and only itch stimuli of medium intensity were applied (extinction) (13).

The current study focuses on the behavioural outcome of scratching. It was hypothesized: (i) that itch amplification by nocebo effects would generalize to enhanced scratching, and (ii) that subsequent reversion of the nocebo effects on itch into placebo effects would generalize to decreased scratching. In addition, this study exploratively investigated whether reversion of the nocebo effects on itch also generalized to scratching associated with an additional itch stimulus (histamine iontophoresis). Frequency of localized scratching was the primary outcome measure, in line with a previous study on evoked itch (17). Frequency of total-body scratching was the secondary outcome measure (16, 18–20). Exploratory, we also analyzed duration of localized and total-body scratching.

Materials and methods

The design and methods have been described in full previously, in our article focusing on reversing nocebo effects in self-reported itch (13). A brief summary is given below.

Participants

A total of 129 healthy participants were included in the study (mean ± standard deviation (SD) age 20.3 ± 2.5 years; 78.7% women). Inclusion criteria were: age range 18–35 years, and fluency in the Dutch language. Exclusion criteria were: severe physical morbidity (e.g. skin disease, diabetes mellitus, multiple sclerosis), psychiatric disorders, chronic itch or pain, diagnosis of histamine hypersensitivity, regular use of medication in the last 3 months, use of a pacemaker, colour blindness, and pregnancy. The study was approved by the medical ethics committee of the Leiden University Medical Center in Leiden, the Netherlands (Commissie Medische Ethiek). All participants provided written informed consent and were reimbursed for their participation.

Study design

The study followed a balanced (1:1:1) randomized controlled, multi-arm parallel-group, double-blind design comprising 3 experimental parts (see Fig. 1 for an overview of the experimental study parts). In Part 1, negative expectations were induced regarding electrical itch stimuli (induction of nocebo effect). In Part 2, participants were randomized over 3 groups in which they received either a positive expectation induction (induction of placebo effect; group 1; n = 33), a continued negative expectation induction (induction of nocebo effect; group 2; n = 34), or an extinction procedure (extinction; group 3; n = 30) with regard to electrical itch stimuli. Both Parts 1 and 2 comprised a learning phase and a testing phase, in which itch stimuli were accompanied by visual cues on a computer screen, i.e. purple and yellow coloured circles. By randomization it was determined whether the conditioned cue was purple or yellow and the neutral cue, consequently, yellow or purple. The following assumes that the conditioned cue is purple and the neutral cue is yellow. In the learning phase of Parts 1 and 2, participants were told that a purple cue would indicate the activation of the third (sham) electrode that increased (nocebo groups) or decreased (placebo groups) the intensity of the itch stimulus. They were also told that the yellow cue would indicate deactivation of the third electrode so the itch stimulus would remain at medium intensity. Conditioning was achieved by applying high (nocebo groups) or low (placebo group) itch stimulus intensities, along with the purple cue (i.e. conditioned trials; 10 stimuli) and medium itch stimulus intensities along with the yellow cue (i.e. neutral trials; 6 stimuli). During the testing phases of Part 1 and 2, all stimuli were given at medium intensity (8 stimuli), while displaying either the purple or yellow cue (both 50% of the trials). In the third part histamine was applied along with the same cue as was used for conditioning in Part 2 (see Fig. 1).

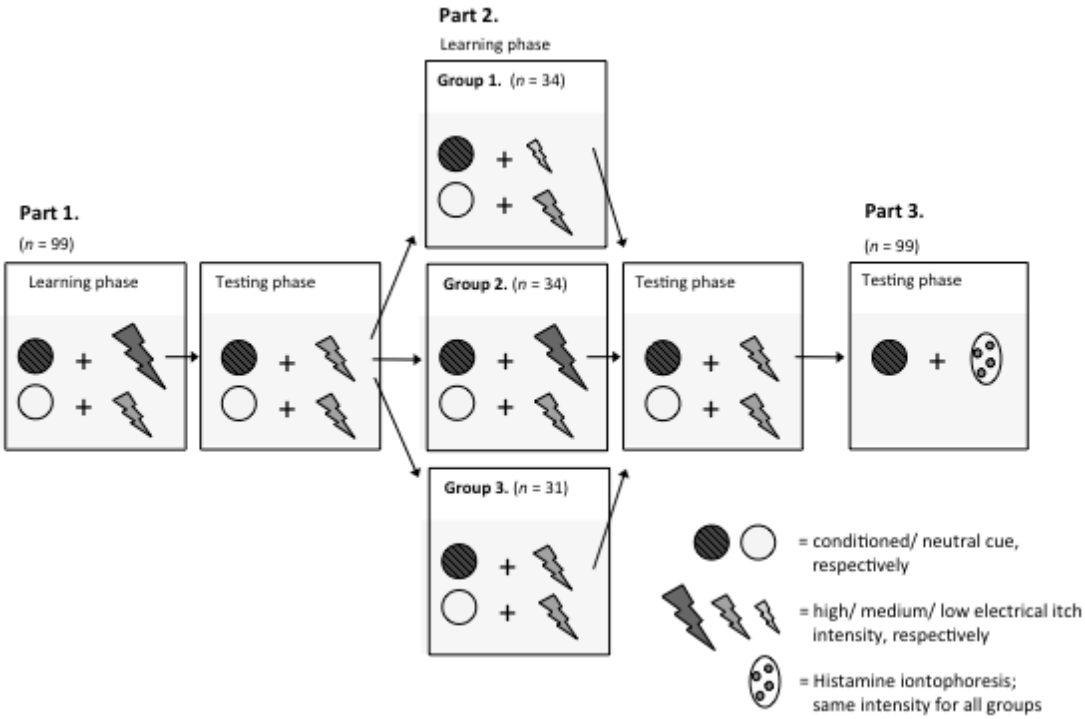

Fig 1. Experimental design. In part 1, negative expectations were induced: participants were told that the purple cue (conditioned cue) indicated an increase in the itch stimulus, and that the yellow cue (neutral cue) indicated no change in the itch stimulus. In accordance, the purple and yellow cues were repeatedly paired with high and medium electrical itch stimulus intensities, respectively. In part 2, participants were randomized over the 3 groups in which (*i*) positive expectations were induced; (*ii*) continued negative expectations were induced; or (*iii*) an extinction procedure was applied. In the learning phases verbal suggestion and conditioning procedures depended on the experimental group. In the testing phases the verbal suggestion corresponded to the verbal suggestion provided in the learning phase, while all participants received electrical itch stimuli of medium intensity. In part 3, for all participants, histamine iontophoresis was applied at the same intensity. The verbal suggestions corresponded with those provided in Part 2, and the purple cue (conditioned cue) was displayed during the histamine application. Note that for half of the participants the conditioned cue was a purple cue and the neutral cue a yellow cue (like in this example); for the other half of the participants the conditioned cue was yellow and the neutral purple.

Itch stimuli

Electrical itch induction. A constant current stimulator (Isolated Bipolar Constant Current Stimulator DS5, Digitimer, Welwyn Garden City, UK) was used to induce itch to the inner side of the non-dominant wrist through 2 surface electrodes. A third (sham) electrode functioned as placebo. Three intensities of itch were individually determined (i.e. low, medium, and high). For the exact procedure see (10). Previous research indicated that itch was the predominant sensation with this induction, and significantly higher than pain (21).

Histamine iontophoresis. Using disposable iontophoresis electrodes (Iogel, Chattanooga, Hixson, TN, USA), 0.6% histamine (as diphosphate) (22) solution (in which histamine content is comparable to 1% histamine dihydrochloride) was delivered with a dose controller (Chattanooga Ionto, Chattanooga) for 2.5 min at a current level of 0.4 mA to the dominant forearm (for the exact procedure see (10)).The same sham electrode used during electrical stimulation served as placebo.

Video-camera and coding software

A video-camera (Panasonic HC-V700, Panasonic Corporation, Osaka, Japan) was located left front of the participant in order to record participants' scratching behaviour. A mirror was located at the right side of the participant to capture an image of the entire body. An event logging software program (The Observer XT 12, Noldus Information Technology bv, Wageningen, The Netherlands) was used to code the scratching responses (see "Coding of scratching behaviour", below).

Procedure

Potential participants were screened for eligibility using online self-report screening questionnaires (Qualtrics, Provo, USA) on demographic variables, and physical and psychological conditions (see (13)). In advance of the laboratory visit, participants were asked to refrain from taking any medication, alcohol, and drugs for at least 24 h before the testing, and from smoking cigarettes or drinking coffee, tea, cola, or energy drinks at least 2 h before testing. At the laboratory visit, the procedures were explained to the participant and informed consent was obtained. Participants were informed that they were being videotaped, although they were given the cover story that the recordings were used for training purposes. Baseline itch, pain, and fatigue were obtained using numerical ratings scales (NRSs) ranging from 0.0 (no itch/pain/ fatigue at all) to 10.0 (most itch/ pain/fatigue ever experienced). After this, the

3 intensities for electrical itch stimulation (i.e. low, medium, and high) were individually determined (see "Electrical itch induction").

In Part 1, negative expectations regarding electrical itch stimuli were induced (induction of nocebo effect, see also Fig. 1). In Part 2, participants were allocated randomly to 1 of 3 groups (see Fig. 1). In the positive expectation induction group (induction of placebo effect; group 1), expectations of low and medium levels of itch were raised in the participants. Thus the meaning of the colour of the conditioned cue was reversed compared with Part 1. In the negative expectation induction group (induction of nocebo effect; group 2), exactly the same nocebo procedure was applied as in Part 1. In the extinction group (extinction; group 3) all stimuli were applied at medium intensity and no verbal suggestion was provided. Participants were merely told that several stimuli would be applied again, accompanied by purple or yellow cues, without being given further details. In Part 3, for all participants, histamine iontophoresis was applied at the same intensity. The verbal suggestions corresponded with those provided in Part 2. Between the stimuli there were standardized inter-stimulus intervals and during the experimental session several standard breaks (13).

Participants were informed 4 times that they were allowed to scratch their itch freely at any time: 3 times during the session with electrical itch stimulation (before determining the individual itch thresholds; before the start of Part 1; and before the start of Part 2) and once before the start of histamine iontophoresis.

At the end of the experiment, participants rated the levels of pain that were induced overall by the electrical itch stimuli on an NRS from 0.0 to 10.0 with a mean ± SD of 1.0 ± 1.2. Finally, saliva was collected for DNA analysis (the results will be reported elsewhere) and participants were asked about their impression of the goal of the study. Almost all participants did not know the true goal of the study.

Coding of scratching behaviour

Spontaneous scratching was coded using the video-recordings by an independent rater who was unaware of the participant's allocation to 1 of 3 groups and the colour of the conditioned and neutral cue. Scratching was defined as any skin contact movement that could reduce itch, e.g. typical scratching using the fingernails, picking with fingernails, or rubbing, while not taking into account touching (16, 20). Regarding the electrical itch stimuli, scratching

behaviour was coded from the start of an itch stimulus up to the next trial (up to 2 min) for the learning and testing phases separately. For the histamine stimulus, scratching behaviour was coded for the 2.5-min duration of the stimulus. Scratching responses were mapped spatially: (i) strictly localized (up to 5 cm around the electrodes); (ii) extended localized on the stimulated arm, excluding strictly localized areas; (iii) extended other arm; (iv) extended head/face/neck; (v) extended torso; and (vi) extended legs. For the preparation of the variables for the analyses, a distinction was made between localized (areas 1 and 2 together) (17) and total-body scratching (areas 1–6 together) (16, 18, 19, 20). Using The Observer software program (The Observer XT 1), frequency (primary outcome) and duration (explorative outcome) of scratching were calculated separately for the different cues and the testing and learning phases.

Statistical analysis

Of the 129 participants tested, data for 97 could be included in the analyses, as 32 were excluded from data analysis on the basis of several pre-determined criteria (see (13)). Specifically, for 8 participants data collection had failed and 24 participants were excluded (with the permission of the local ethics committee) because they experienced no or too little itch after repeated electrical itch induction (for details see (13)). However, sensitivity analyses were also carried out for all 121 participants, including those in whom levels of evoked itch were low but scratching data were available.

In line with the main aims, for all outcomes, frequency of localized scratching was regarded as the primary outcome, frequency of total-body scratching was regarded as the secondary outcome and duration of localized and total-body scratching was analysed exploratively. Means of scratching were calculated for both conditioned (i.e. with the supposed activation of the third electrode) and neutral trials (i.e. without the supposed activation of the third electrode) for the learning and testing phases. The nocebo effect on scratching was defined as the difference between scratching episodes associated with the conditioned trials and neutral trials. The higher the score the higher was the nocebo effect.

To explore the efficacy of the nocebo expectation induction procedure during the learning phase in Part 1, scratching episodes associated with the conditioned and neutral trials were compared in paired samples t-tests. Also, to test the hypothesis that there was a nocebo effect on scratching in the testing phase of Part 1, paired samples t-tests were performed.

The efficacy of the expectation induction procedure in the learning phase of Part 2 was assessed exploratively by univariate analyses of variance (ANOVA) with group as between-subject factor and scratching as dependent variable. Similar ANOVAs were performed for the testing phase of Part 2 when testing the hypothesis that the positive expectation induction group would display a significantly smaller nocebo effect with regard to scratching than the control groups (negative expectation induction group and extinction group). A similar approach was taken to exploratively assess generalization of the reversion of nocebo effects on itch to scratching during the histamine stimulus, whilst including the scratching scores during histamine iontophoresis.

Where the assumptions of the statistical tests (e.g. of normality) were violated, sensitivity analyses were conducted by calculating bias-corrected 95% confidence intervals (95% CIs) around the relevant parameter using 1,000 bootstrapping samples (23). This was the case for the duration of localized scratching in the testing phase of Part 1, as well as the frequency and duration of localized scratching behaviour in the testing phase of Part 2. Since bootstrapped confidence intervals around the parameters provided results similar to those reported without bootstrapping, we reported the non-bootstrapped analyses.

All analyses were performed using SPSS 23.0 for Windows (IBM SPSS Statistics, Chicago, IL, USA) and the level of statistical significance was set at $p < 0.05$ (2-sided). Unless displayed otherwise, results are displayed as means ± SD.

RESULTS

In Part 1 (induction of nocebo effect), negative expectations were induced in all participants. In Part 2 (reversal of nocebo effect), randomization of the participants across the 3 groups resulted in a total of 33 participants in the positive expectation induction group, 34 participants in the negative expectation induction group, and 30 participants in the extinction group. The groups did not differ significantly on baseline characteristics (Table I).

Table I. Participant characteristics

	Group 1 - Positive expectation induction n = 33	*Group 2 - Negative expectation induction n = 34*	*Group 3 - Extinction n = 30*
Age, years, mean ± SD	20.3±2.6	20.3±2.7	20.0±2.0
Male/female ratio %	27.3/72.7%	23.5/76.5%	20.0/80.0%
Hormonal contraceptives %	42.4%	50.0%	56.7%
Itch baseline test day NRS, mean ± SD	0.6±0.8	0.6±0.7	0.6±0.7
Pain baseline test day NRS, mean ± SD	0.4±0.7	0.4±0.5	0.5±0.7
Fatigue baseline test day NRS, mean ± SD	2.4±1.6	2.1±1.5	2.1±1.3
Itch baseline histamine NRS, mean ± SD	1.0±1.1	0.9±1.1	0.7±0.7
Pain baseline histamine NRS, mean ± SD	0.6±1.0	0.6±0.6	0.5±0.7
Fatigue baseline histamine NRS, mean ± SD	3.6±1.7	3.6±1.3	3.8±1.5

SD: standard deviation; NRS: Numeric rating scale.

Induction of negative expectations (Part 1)

Learning phase. During the learning phase of Part 1 (Table II), in which negative expectations were induced for all participants by both verbal suggestion and conditioning, as expected, the paired samples t-tests revealed that means for the conditioned trials were significantly higher than for the neutral trials for the frequency of localized scratching ($t(96) = 3.89$, $p < 0.001$, $d = 0.395$), duration of localized scratching ($t(96) = 4.13$, $p < 0.001$, $d = 0.420$), and duration of total-body scratching ($t(96) = 3.07$, $p < 0.01$, $d = 0.312$). The frequency of total-body scratching was marginally significantly higher for the conditioned vs. neutral trials ($t(96) = 1.94$ $p = 0.056$, $d = 0.196$).

Testing phase. When testing whether there was a nocebo effect during the testing phase of Part 1 (Table II), in which all stimuli were applied at medium intensity, the paired samples t-test revealed that means for the conditioned trials were marginally significantly higher than for the neutral trials for frequency of localized scratching ($t(96) = 1.77$, $p = 0.081$, $d = 0.179$) and duration of localized scratching ($t(96) = 1.77$, $p = 0.079$, $d = 0.180$). No significant nocebo effect was found for total-body scratching regarding the frequency ($t(96) = 0.63$, $p = 0.53$, $d = 0.064$) and duration ($t(96) = 1.46$, $p = 0.15$, $d = 0.148$).

Table II. Means (±*SD)* of mean frequency and duration of scratching episodes in the learning and testing phase in Part 1 (induction of negative expectations)

		Learning phase				***Testing phase***			
		Conditioned trials	Neutral trials			Conditioned trials	Neutral trials		
		M±SD	M±SD	*p-value*	*d*	M±SD	M±SD	*p*-value	*d*
Localized scratching	*Frequency*	0.6±0.7	0.4±0.6	<0.001	0.395	0.3±0.4	0.3±0.4	0.081	0.179
	Duration	2.5±4.3	1.8±3.8	<0.001	0.420	1.1±2.0	0.9±1.7	0.079	0.180
Total-body scratching	*Frequency*	1.9±1.2	1.8±1.0	0.056	0.196	1.7±1.3	1.6±1.2	0.53	0.064
	Duration	5.1±5.8	4.3±4.8	<0.001	0.312	3.7±4.0	3.4±3.9	0.15	0.148

Means (*M*) and standard deviations (*SD*) of mean frequency and mean duration (in seconds) of scratching episodes in the learning and testing phase in Part 1 (induction of negative expectations; *n=97*). Localized scratching episodes comprised scratching limited to the arm where the itch stimulus was applied. Total-body scratching episodes comprised scratching over the whole body (including localized scratching).

Reversal of nocebo effect (Part 2)

Learning phase. Table III displays the mean ± SD frequency and duration of the scratching episodes evoked by the itch stimuli associated with the conditioned and neutral trials during the learning phases for each group, in which depending on the group, positive (group 1) or negative (group 2) expectations were induced or an extinction procedure (group 3) was applied. When testing whether the mean change score (conditioned trials minus neutral trials) of scratching episodes was smaller in the positive expectation induction group (group 1) than in the control groups (groups 2 and 3), ANOVAs did not reveal a significant group difference for any of the outcome measures: frequency of localized scratching ($F(2,96) = 1.37$, $p = 0.259$ $\eta_p^2 = 0.028$), frequency of total-body scratching ($F(2,96) = 2.09$, $p = 0.130$, $\eta_p^2 = 0.042$), duration of localized scratching ($F(2,96) = 1.43$, $p = 0.244$ $\eta_p^2 = 0.030$) and duration of total-body scratching ($F(2,96) = 0.95$, $p = 0.391$, $\eta_p^2 = 0.020$).

Table III. Means (±SD) of mean frequency and duration (s) of scratching episodes in the learning phase in Part 2

		Group 1 *- Positive expectation induction*		***Group 2*** *– negative expectation induction*		***Group 3*** *– Extinction*			
		Conditio-ned trials	Neutral trials	Conditio-ned trials	Neutral trials	Conditio-ned trials	Neutral trials		
		Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	*p*-value	*d*
Localized Scratching	*Frequency*	0.3±0.4	0.4±0.5	0.3±0.4	0.2±0.3	0.4±0.4	0.4±0.5	0.259	0.028
	Duration	0.9±1.2	1.2±1.4	1.1±1.9	1.0±1.	1.5±1.9	1.3±1.8	0.244	0.030
Total-body scratching	*Frequency*	1.7±1.1	1.5±0.9	1.9±1.2	1.6±1.0	1.6±0.9	1.7±0.9	0.130	0.042
	Duration	3.8±3.0	3.5±3.0	3.8±2.7	3.3±2.5	3.8±3.9	3.9±4.1	0.391	0.020

Means ± standard deviations (*SD*) of mean frequency and mean duration (in s) of scratching episodes and for the change in scratching score (scratching frequency / duration score of the conditioned trials minus the neutral trials) in the *positive expectation induction group* (group 1; *n*=33), the *negative expectation induction group* (group 2; *n*=34) and the *extinction group* (group 3; *n*=30) in the learning phase of Part 2. Localized scratching episodes comprised scratching limited to the arm where the local itch stimulus was applied. Total-body scratching episodes comprised scratching over the whole body (including localized scratching).

Testing phase. Table IV displays the mean ± SD frequency and duration of the scratching episodes evoked by the itch stimuli associated with the conditioned and neutral trials during the testing phase for each group, in which all stimuli were applied at medium intensity. When testing the hypothesis that the nocebo effect on frequency of localized scratching was smaller in the positive expectation induction group than in the control groups, univariate ANOVA showed no significant difference in the magnitude of the nocebo effect ($F(2,96) = 0.36$, $p = 0.697$ $\eta_p^2 = 0.008$). Also, for the frequency of total-body scratching (secondary outcome) no significant difference between the groups was observed ($F(2,96) = 0.90$, $p = 0.409$ $\eta_p^2 = 0.019$). Furthermore, also regarding duration of scratching episodes, no significant difference in localized scratching ($F(2,96) = 0.78$, $p = 0.463$ $\eta_p^2 = 0.016$) or total- body scratching ($F(2,96) = 1.30$, $p = 0.279$ $\eta_p^2 = 0.027$) was found between the groups.

Table IV. Mean frequency and duration *(s)* of scratching episodes in the testing phase in Part 2

		Group 1 *- Positive expectation induction*		***Group 2*** *– negative expectation induction*		***Group 3*** *– Extinction*			
		Conditio-ned trials	Neutral trials	Conditio-ned trials	Neutral trials	Conditio-ned trials	Neutral trials		
		Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	*p*-value	*d*
Localized Scratching	*Frequency*	0.3±0.4	0.3±0.5	0.2±0.3	0.3±0.4	0.3±0.3	0.2±0.3	0.697	0.008
	Duration	0.7±1.1	1.0±1.8	0.6±1.0	0.8±1.6	0.7±1.2	0.7±0.9	0.463	0.016
Total-body scratching	*Frequency*	1.4±1.0	1.6±0.9	1.7±1.0	1.7±0.8	1.6±1.0	1.6±0.9	0.409	0.019
	Duration	2.5±1.9	3.4±2.5	3.1±2.3	3.3±2.5	3.2±3.3	3.2±2.6	0.279	0.027

Means and standard deviations (*SD*) of mean frequency and mean duration (in s) of scratching episodes and for the change in scratching score (scratching frequency / duration score of the conditioned trials minus the neutral trials) in the *positive expectation induction group* (group 1; *n*=33), the *negative expectation induction group* (group 2; *n*=34) and the *extinction group* (group 3; *n*=30) in the testing phase of Part 2. Localized scratching episodes included scratching limited to the arm where the local itch stimulus was applied. Total-body scratching episodes included scratching over the whole body (including localized scratching).

Generalization of revered nocebo effects on itch to scratching behaviour for histamine iontophoresis

When exploring scratching behaviour during the histamine stimulus (Table V), ANOVAs showed no significant effect of group regarding the frequency of localized scratching ($F(2,96) = 0.62$, $p = 0.54$, $\eta_p^2 = 0.013$), frequency of total-body scratching episodes ($F(2,96) = 0.56$, $p = 0.57$, $\eta_p^2 = 0.012$), duration of localized scratching episodes ($F(2,96) = 0.32$, $p = 0.73$, $\eta_p^2 = 0.007$), or duration of total-body scratching episodes ($F(2,96) = 0.25$, $p = 0.77$, $\eta_p^2 = 0.005$).

Sensitivity analyses

When exploring the influence of excluding the data of the 24 participants who experienced little to no itch after repeated electrical itch induction (<1 itch on NRS), sensitivity analysis with all 121 participants for whom scratching data were available generally obtained results similar to those for the 97 participants, with some exceptions. Specifically, in the testing phase of Part 1, instead of a marginally significant difference, results revealed a

significantly higher mean ± SD frequency of localized scratching episodes for the conditioned trials (0.3 ± 0.4) than for the neutral trials (0.2 ± 0.3) ($t(120) = 2.36$ $p < 0.05$, $d = 0.214$), and a longer mean duration of localized scratching episodes for the conditioned trials (1.0 ± 1.8) than for the neutral trials (0.8 ± 1.5) ($t(120) = 2.27$, $p < 0.05$, $d = 0.206$). In the testing phase of Part 2, instead of a non-significant difference, there was a tendency towards significance in the magnitude of the nocebo effect of duration of total-body scratching between the positive expectation induction group and the control groups ($F(2, 120) = 2.78$, $p = 0.066$, $\eta_p^2 = 0.045$).

Table V. Mean frequency and duration *(s)* of scratching episodes during application of histamine

		Group 1 *- Positive expectation induction*	***Group 2*** *- negative expectation induction*	***Group 3*** *- Extinction*		
		Mean ± SD	Mean ± SD	Mean ± SD	*p*-value	*d*
Localized scratching	*Frequency*	2.6±3.4	1.8±2.5	2.6±3.6	0.54	0.013
	Duration	13.8±23.0	9.8±17.6	12.5±22.3	0.57	0.012
Total-body scratching	*Frequency*	3.2±3.5	2.3±2.7	2.7±3.7	0.73	0.007
	Duration	14.7±23.3	11.0±18.1	12.6±22.3	0.77	0.005

Means and standard deviations (*SD*) of mean frequency and mean duration (in s) of scratching episodes during the application of the histamine stimulus (which takes approximately 2.5 min) in the *positive expectation induction group* (group 1; *n*=33), the *negative expectation induction group* (group 2; *n*=34) and the *extinction group* (group 3; *n*=30). Localized scratching episodes included scratching limited to the arm where the local itch stimulus was applied. Total-body scratching episodes included scratching over the whole body (including localized scratching).

DISCUSSION

The present study investigated, for the first time, the generalizability of induced nocebo effects on itch to scratching behaviour. First, results showed that, while manipulating the itch intensity during the nocebo learning phase, participants scratched more often and for a longer duration when itch stimuli of a higher intensity were applied than when itch stimuli of medium intensity were applied. However, this did not lead to subsequent significant nocebo effects on scratching behaviour in the testing phase, apart from some marginal significant effects.

Secondly, reversing nocebo effects on itch by positive expectation induction, did not lead to reversed or reduced nocebo effects on scratching behaviour. Sensitivity analysis in a larger group of participants did show some significant nocebo effects on scratching and a tendency for reduced nocebo effects on scratching. We can conclude that, although higher itch intensity is associated with more scratching, no conclusive evidence for generalization of nocebo effects on itch to scratching was found.

Exposing participants to itch stimuli of high intensity (in the learning phase of nocebo induction) resulted in significantly more frequent scratching, and scratching for a longer duration, around the specific area of the forearm where itch was induced compared with itch stimuli of medium intensity. When we assessed scratching behaviour all over the body, similar findings were obtained, with significant results for duration and marginally significant results for frequency of scratching behaviour. Thus, when itch stimuli of higher intensity are applied compared with itch stimuli of lower intensity, participants not only experienced more itch (13), they mostly also displayed increased scratching behaviour, indicating a correspondence between self-report outcomes and observable behaviour (3, 18). This further supports that scratching behaviour can objectively be measured and is related to the intensity of itch (16, 18, 19).

Our hypothesis that nocebo effects on itch generalize to scratching could not be confirmed. Negative expectation induction for high levels of itch regarding stimuli of medium intensity (in the testing phase of part 1) did not result in significant nocebo effects on scratching. Also positive expectation induction for low levels of itch regarding stimuli of medium intensity (in the testing phase of part 2) did not result in significantly smaller nocebo effects on scratching for both the electrical and histamine stimuli compared with the control groups. These findings are unexpected, since our study did show significant nocebo effects on self-reported itch after negative expectation induction, and significantly reduced nocebo effects on itch after positive expectation induction when electrical or histamine itch stimuli were applied (13). A possible explanation for the non-significant results on scratching might be that, in our study, no verbal suggestions were provided for scratching, but only for itch, which is a pure way to assess generalizability of the nocebo effects on itch. Similar results were obtained in a recent study on itch perception modulated by verbal suggestion in healthy participants (24). This study demonstrated an increase in itch perception in a nocebo-like

condition, but no increase in the desire to scratch. Actual scratching behaviour was not measured (24). Furthermore, in studies regarding contagious itch, i.e. itch evoked by audio-visual stimuli, inductions of expectation often indirectly address itch and especially scratching, e.g. by showing participants videos of people scratching (16–18, 20). This is, for example, confirmed by a study by Lloyd et al. (19) demonstrating that pictures of itch-relevant stimuli, e.g. insects crawling on skin, resulted in increased itch in healthy subjects than did pictures of people scratching, whereas pictures of people scratching led to more scratching behaviour than the itch-relevant pictures (19). Previous studies investigating generalizability of placebo or nocebo effects on symptoms other than itch all included verbal suggestions for the second modality. For example, a study on pain showed that conditioned nocebo effects in pain tolerance can be transferred to motor endurance; however, verbal suggestions for decreased motor endurance were also provided (25). Other studies on pain that demonstrated transferable placebo effects from pain to emotion have also provided verbal suggestions regarding alleviation of negative emotions (26–28). It is likely that the generalized placebo and nocebo effects are partly explained by additional verbal suggestions for the second modality. Another possible explanation for the lack of generalized nocebo effects on scratching in the current study could be that the levels of itch did not always reach the threshold at which participants felt the urge to scratch (15). Future research should investigate whether directly targeting scratching behaviour by induction of expectation is required to induce and reverse nocebo effects on scratching.

When comparing healthy participants with patients with chronic itch conditions, several studies have shown that patients scratch more frequently than healthy participants when an experimental itch stimulus is applied (17, 20), even when stimulus intensity and self-reported itch do not significantly differ for both patients and healthy participants (20). This is underlined by neuroimaging studies that demonstrate that different brain areas are activated in patients with chronic itch and healthy participants when itch stimuli are applied (29–31). For example, a study in patients with atopic dermatitis showed that, even though there were no significant differences in perceived itch, brain activation in areas that are assumed to correspond to scratching differed between the patients and healthy participants (29). Such differences may also play a role in placebo and nocebo effects on scratching and therefore placebo and nocebo effects on scratching should be investigated in patients with chronic itch.

Some possible limitations and further suggestions for future research should be discussed. First, participants might have been hindered in spontaneous scratching due to the filler tasks that were provided between the different itch stimuli. Since the electrodes were attached to the non-dominant arm, participants were not able to scratch around the itch-induced area of the forearm with the non-dominant hand, but only with their dominant hand. However, participants mainly used their dominant hand for completing the filler tasks and had to pause performing the tasks in order to scratch their itch. It is possible that this led to reduced scratching in participants. Future studies should consider inter-stimulus intervals with tasks whereby participants do not use their hand and are able to scratch without any constraints. Secondly, participants tended to report less itch as the experiment progressed (13). It could be that the decline in itch resulted in less often reaching the participants' itch threshold (15) (especially in the testing phase of Part 1 and the learning and testing phase of Part 2), which could have influenced the scratching results. Thirdly, since we were interested mainly in whether nocebo effects on itch generalize to scratching behaviour, we did not directly compare localized and extended scratching behaviour (such as (17)). Given that, for contagious itch, people do not seem to scratch the same area as the area observed in the manipulation video (i.e. area on the body where the person in the manipulation video scratches), future research could manipulate the location of itch to determine whether nocebo effects on scratching are mainly localized or extended.

In conclusion, this study confirms that scratching behaviour can be used as a measure of itch in healthy participants. No conclusive evidence was found for the generalization of nocebo effects on itch to scratching; however, sensitivity analysis in a larger group of participants showed some preliminary effects or tendencies that nocebo effects on itch can generalize to scratching. Future research should investigate generalization of (reversed) placebo and nocebo effects from itch to scratching, especially when high levels of itch are experienced, exceeding specific itch thresholds that lead to scratching, and also when involving patients with chronic itch. From the clinical viewpoint, studying how a placebo effect can generalize from one domain to another may be important to increase the effectiveness of treatments for all kinds of conditions that often comprise symptoms in different modalities. The possibility of reducing symptoms in one modality, i.e. scratching behaviour, using training in another modality, i.e. itch, could possibly be applied in dermatological conditions associated

with chronic itch and scratching. Therefore, greater understanding of the generalization of placebo and nocebo effects on itch to scratching behaviour could be important to determine ways to enhance treatments for chronic itch in clinical practice.

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References

Matterne U, Strassner T, Apfelbacher CJ, Diepgen TL, Weisshaar E. Measuring the prevalence of chronic itch in the general population: development and validation of a questionnaire for use in large-scale studies. Acta Derm Venereol 2009; 89: 250–256.

Yosipovitch G, Papoiu AD. What causes itch in atopic dermatitis? Curr Allerg Asthma Rep 2008; 8: 306–311.

Verhoeven EW, de Klerk S, Kraaimaat FW, van de Kerkhof PC, de Jong EM, Evers AW. Biopsychosocial mechanisms of chronic itch in patients with skin diseases: a review. Acta Derm Venereol 2008; 88: 211–218.

Grundmann S, Stander S. Chronic pruritus: clinics and treatment. Ann Dermatol 2011; 23: 1–11.

Bartels DJ, van Laarhoven AI, van de Kerkhof PC, Evers AW. Placebo and nocebo effects on itch: effects, mechanisms, and predictors. Eur J Pain 2016; 20: 8–13.

van Laarhoven AI, van der Sman-Mauriks IM, Donders AR, Pronk MC, van de Kerkhof PC, Evers AW. Placebo effects on itch: a meta-analysis of clinical trials of patients with dermatological conditions. J Invest Dermatol 2015; 135: 1234–1243.

Benedetti F. Mechanisms of placebo and placebo-related effects across diseases. Ann Rev Pharmacol 2008; 48: 33–60.

Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. Psychosom Med 2011; 73: 598–603.

Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. Annu Rev Psychol 2008; 59: 565–590.

Bartels DJ, van Laarhoven AI, Haverkamp EA, Wilder-Smith OH, Donders AR, van Middendorp H, et al. Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. PLoS One 2014; 9: e91727.

van Laarhoven AI, Vogelaar ML, Wilder-Smith OH, van Riel PL, van de Kerkhof PC, Kraaimaat FW, et al. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain 2011; 152: 1486–1494.

Petersen GL, Finnerup NB, Colloca L, Amanzio M, Price DD, Jensen TS, et al. The magnitude of nocebo effects in pain: a meta-analysis. Pain 2014; 155: 1426–1434.

Bartels DJP, van Laarhoven AIM, Stroo M, Hijne K, Peerde-man KJ, Donders ART, et al. Minimizing nocebo effects by conditioning with verbal suggestion: a randomized clinical trial in healthy humans. PLoS One 2017; 12: e0182959.

Ikoma A, Steinhoff M, Stander S, Yosipovitch G, Schmelz M. The neurobiology of itch. Nat Rev Neurosci 2006; 7: 535–547.

Savin JA. How should we define itching? J Am Acad Dermatol 1998; 39: 268–269.

Schut C, Muhl S, Reinisch K, Classen A, Jager R, Gieler U, et al. Agreeableness and self-consciousness as predictors of induced scratching and itch in patients with psoriasis. Int J Behav Med 2015; 22: 726–734.

Papoiu AD, Wang H, Coghill RC, Chan YH, Yosipovitch G. Contagious itch in humans: a study of visual 'transmission' of itch in atopic dermatitis and healthy subjects. Br J Dermatol 2011; 164: 1299–1303.

Holle H, Warne K, Seth AK, Critchley HD, Ward J. Neural basis of contagious itch and why some people are more prone to it. Proc Natl Acad Sci U S A 2012; 109: 19816–19821.

Lloyd DM, Hall E, Hall S, McGlone FP. Can itch-related visual stimuli alone provoke a scratch response in healthy individuals? Br J Dermatol 2013; 168: 106–111.

Schut C, Bosbach S, Gieler U, Kupfer J. Personality traits, depression and itch in patients with atopic dermatitis in an experimental setting: a regression analysis. Acta Derm Venereol 2014; 94: 20–25.

Andersen HH, van Laarhoven AIM, Elberling J, Arendt-Nielsen L. Modulation of Itch by conditioning itch and pain stimulation in healthy humans. J Pain 2017; 18: 1437–1450.

van Laarhoven AI, Ulrich DJ, Wilder-Smith OH, van Loey NE, Nieuwenhuis M, van der Wee NJ, et al. Psychophysiological processing of itch in patients with chronic post-burn itch: an exploratory study. Acta Derm Venereol 2016; 96: 613–618.

Hayes AF, Scharkow M. The relative trustworthiness of inferential tests of the indirect effect in statistical mediation analysis: does method really matter? Psychol Sci 2013; 24: 1918–1927.

Stumpf A, Zerey V, Heuft G, Stander S, Pfleiderer B, Schneider G. Itch perception and skin reactions as modulated by verbal suggestions: role of participant's and investigator's sex. Acta Derm Venereol 2016; 96: 619–623.

Carlino E, Guerra G, Piedimonte A. Placebo effects: from pain to motor performance. Neurosci Lett 2016; 632: 224–230.

Zhang W, Luo J. The transferable placebo effect from pain to emotion: changes in behavior and EEG activity. Psycho- physiology 2009; 46: 626–634.

Zhang W, Qin S, Guo J, Luo J. A follow-up fMRI study of a transferable placebo anxiolytic effect. Psychophysiology 2011; 48: 1119–1128.

Zhang W, Luo J. Neural bases of reappraisal regulatory effect on negative emotion in high reappraisers. Neural Regen Res 2012; 7: 2542–2547.

Schneider G, Stander S, Burgmer M, Driesch G, Heuft G, Weckesser M. Significant differences in central imaging of histamine-induced itch between atopic dermatitis and healthy subjects. Eur J Pain 2008; 12: 834–841.

Ishiuji Y, Coghill RC, Patel TS, Oshiro Y, Kraft RA, Yosipovitch G. Distinct patterns of brain activity evoked by histamine-induced itch reveal an association with itch intensity and disease severity in atopic dermatitis. Br J Dermatol 2009; 161: 1072–1080.

Mochizuki H, Papoiu ADP, Yosipovitch G. Brain processing of itch and scratching. In: Carstens E, Akiyama T, editors. Itch: mechanisms and treatment. Boca Raton, FL: CRC Press, Taylor & Francis group 2014, pp 391–408.

CHAPTER 6

COGNITIVE SCHEMAS IN PLACEBO AND NOCEBO RESPONDING: ROLE OF AUTOBIOGRAPHICAL MEMORIES AND EXPECTATIONS

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Abstract

Purpose: Placebo effects are presumed to be based on one's expectations and previous experience with regard to a specific treatment. The purpose of this study was to investigate the role of the specificity and valence of memories and expectations with regard to itch in experimentally induced placebo and nocebo itch responses. It was expected that cognitive schemas with more general and more negative memories and expectations with regard to itch contribute to less placebo itch responding.

Methods: Validated memory tasks (ie, the Autobiographical Memory Test and the Self-referential Endorsement and Recall Task) and expectation tasks (ie, Future Event Task and the Self-referential Endorsement and Recall Task) were modified for physical symptoms, including itch. Specificity and valence of memories and expectations were assessed prior to a placebo experiment in which expectations regarding electrical itch stimuli were induced in healthy participants.

Findings: Participants who were more specific in their memories regarding itch and who had lesser negative itch-related expectations for the future were more likely to be placebo itch responders. There were no significant differences in effects between the nocebo responders and nonresponders.

Implications: The adapted tasks for assessing cognitive (memory and expectations) schemas on itch seem promising in explaining interindividual differences in placebo itch responding. Future research should investigate whether similar mechanisms apply to patients with chronic itch. This knowledge can be used for identifying patients who will benefit most from the placebo component of a treatment.

Introduction

Placebo and nocebo effects are known to contribute to overall treatment outcomes in various conditions and symptoms (eg, pain, itch).[1] Whereas it is known that specific learning mechanisms (eg, conditioning) in general can result in placebo and nocebo effects, placebo and nocebo responses vary tremendously among individuals.[2,3] In both experimental and clinical studies, individuals' placebo or nocebo responses have been shown to range from no effect to profound changes in symptoms or disease outcomes.[4,5] Several studies have tried to identify the "placebo responder", but this remains a challenge.[6] Although the respective literature is still limited and inconsistent,[6] certain traits have been proposed to contribute to placebo and nocebo responding, such as psychological traits, including optimism, neuroticism, or catastrophizing[7–9]; genetic predispositions[10]; and cognitive factors, including cognitive schemas (ie, mental structure in which thoughts, information, and their inter-relationships are categorized) of memory about the past and expectations about the future.[11]

Assessments of cognitive schemas of memories and expectations have shown that dimensions of specificity and valence of memories and expectations are of particular importance. With regard to specificity of memories and expectations, overgeneral autobiographical memory, defined as difficulty in retrieving specific autobiographical memories, has been shown to be related to depression and trauma-related psychopathology[12] and difficulties with social problem solving[13] but specificity of autobiographical memory has never been investigated with regard to placebo and nocebo responses. With regard to valence of memories and expectations, positive previous experiences and positive expectations regarding a particular treatment are related to greater placebo responding, and negative previous experiences and negative expectations are related to greater nocebo responding.[14–16] Furthermore, prior stimulus history can have an influence on placebo response.[17,18] For example, results from a study by Geers et al[17] showed that previous experience with a pain stimulus (cold pressor task) in daily life (pain trough contact with cold water) reduced the effectiveness of placebo analgesic expectation.

In the current study we sought to determine whether specificity and valence of memories and expectations are associated with placebo and nocebo itch responses. To answer this question, specificity and valence of participants' memories and expectations regarding itch were assessed prior to a placebo and nocebo itch experiment in which

expectations were induced by conditioning and verbal-suggestion procedures (see Bartels et al[16]). Both specificity and valence of memories and expectations were assessed with validated tasks modified for itch by our research group. We expected that, in particular, participants with more specific and more positive memories and expectations would show greater placebo responses, while participants with less specific and more negative memories and expectations would be more likely to show nocebo responses. Furthermore, it was explored whether specificity and valence of itch-related memories were related to specificity and valence of itch-related expectations, respectively.

PATIENTS AND METHODS

Data were obtained in a single study, from which outcomes on the induction of placebo and nocebo effects on itch by different expectation inductions have been reported previously.[16] The present study focused on the influence of individual cognitive schemas on placebo and nocebo itch responses. The methods (and data) concerning the cognitive schemas have not been described in the previous study. The methods concerning the induction of placebo and nocebo effects, and general preparatory steps, have previously been described[16] and are briefly summarized here.

Ethics Statement

The study protocol was approved by a regional medical ethics committee (CMO Arnhem-Nijmegen, Nijmegen, the Netherlands) and follows the principles stated in the Declaration of Helsinki. All participants provided written informed consent and were reimbursed for their participation.

Participants

Healthy volunteers aged ≥18 years were recruited via an online research participant system (Sona Systems, Tallinn, Estonia) and at the Radboud University Nijmegen (Nijmegen, the Netherlands). Inclusion criteria were age ≥18 years and fluency in the Dutch language. Exclusion criteria were severe morbidity (eg, skin disease, multiple sclerosis, diabetes mellitus), psychiatric disorders (eg, depression), color blindness, regular use of medication in the preceding 3 months, use of pacemaker, pregnancy, and current or a history of chronic itch or pain.

Study Design

The study comprised 2 sessions in the laboratory, separated by ≥1 week. During session 1, participants' cognitive schemas (ie, specificity and valence of memories and expectations regarding itch-related, pain-related, and standard events) were assessed. Specificity of memories was assessed with the Autobiographical Memory Test (AMT); specificity of future expectations, with the Future Event Task (FET); valence of memories and future expectations, with the Self-referential Endorsement and Recall Task (SER).

During session 2, placebo and nocebo effects of electrically induced itch were assessed. Participants were randomized to 1 of 4 groups in which they received either: (1) verbal suggestion; (2) conditioning; (3) a combination of verbal suggestion and conditioning to induce expectations for low, medium, and high itch intensity (intervention groups); or (4) a control procedure (control group) (see Bartels et al[16]).

General Procedures

Recruitment was conducted by an online research-participant system (Sona Systems, Tallinn, Estonia) and through flyers posted at Radboud University. Eligibility of potential participants was determined by means of online self-report screening questionnaires, assessed by Sona Systems (Tallinn, Estonia).

Session 1

At the first laboratory visit (session 1), written informed consent was obtained, and baseline itch, pain, and fatigue were assessed using numeric rating scales (NRSs) ranging from 0.0 (no itch/pain/fatigue at all) to 10.0 (worst itch/pain/fatigue ever experienced). Subsequently, the adapted AMT, FET, and SER were administered in a randomized order. Also their sub-tasks (itch, pain, and traditional (with emotional cue words)) were administered in a randomized order.

Tasks Assessing Cognitive Schemas

Autobiographical Memory Test

The AMT was used for assessing the specificity of memories of participants regarding specific cue words. Three different versions of the AMT were administered in this study: the traditional version (AMT-t)19; a version for itch developed by our research group (AMT-i); and one for pain developed by our research group (AMT-p). The AMT-i was the focus of this study.

In all versions of the AMT, the cue words were consecutively, but in randomized order, presented verbally, and participants were asked to recall and write down a memory in response to each cue word.[20] Participants were instructed to write down an autobiographical memory, that is, a personally experienced event, that happened any time in the past, but not on the day of or the day before the administration of the instrument. The event could be important or not. Participants were asked not to write down the same event twice. In accordance with the Minimal Instructions version of the AMT,[21] which is more sensitive for detecting reduced specificity of autobiographical memory in nonclinical individuals than is the standard version, participants were not explicitly asked to come up with a specific memory but were merely asked "Can you write down an event that the word X reminds you of?". No examples of correct or incorrect responses were given and no practice items were provided. Participants were given 60 seconds per cue word to write down a memory.

The AMT-t consisted of 6 positive and 6 negative emotional cue words (eg, happy or sad)[19] (see Supplemental Appendix 1). The AMT-i consisted of 9 itch-related cue words (Table I). The instructions were identical to those of the traditional AMT, but the participants were explicitly asked to write down a memory concerning itch. The AMT-p consisted of 9 pain-related cue words (see Supplemental Appendix 1) and the participants were explicitly asked to write down a memory concerning pain.

The cue words used for the AMT-i and AMT-p (also the FET-i and FET-p; see subsequent text) had been collected from the itch and pain questionnaires, online patient panels, and input from a group of volunteers with chronic itch and/or pain symptoms. Subsequently, this large pool of words was scored by 5 independent raters on: (1) applicability to itch/pain (applicable to itch, pain, or neither); (2) familiarity, ranging from 0 (completely unfamiliar) to 5 (completely familiar); and (3) conceivability, ranging from 0 (completely not conceivable) to 5 (completely conceivable). The 18 words that scored the highest on the 3 scales for itch were used in the AMT-i and FET-i, and the 18 words that scored the highest on the 3 scales for pain were used in the AMT-p and FET-p.

Table I. Cue words of the itch version of the adapted Autobiographical Memory Task (AMT-i) and the adapted Future Event Task (FET-i).*

AMT-i	FET-i
Itch remedy *(middel tegen jeuk)*	Dry skin *(droge huid)*
Sunburn peeling *(vervellen)*	Scratch open *(openkrabben)*
Rubbing *(wrijven)*	Itchy *(jeukend)*
Mosquito bite *(muggenbult)*	Nettle *(brandnetel)*
Itchy spot *(plek die jeukt)*	Bumps *(bultjes)*
Scratching *(krabben)*	Tickling *(kriebelen)*
Wool *(wol)*	Allergy *(allergie)*
Eczema *(Eczeem)*	Skin *(huid)*
Rash *(huiduitslag)*	Itch *(Jeuk)*

* Original cue words in Dutch are shown in parantheses.

Future Event Task

The FET was used for assessing the specificity of future expectations of participants regarding specific cue words. Three different versions of the FET were administered in this study: the traditional version (FET-t)[22]; a version for itch developed by our research group (FET-i); and one for pain developed by our research group (FET-p). The FET-i was the focus of this study.

In the 3 versions of the FET, the cue words were consecutively, but in randomized order, presented verbally, and participants were asked to write down an expectation in response to each cue word. Participants were instructed to write down an autobiographical expectation, that is, an expectation of an event that can be personally experienced, which can happen at any time in the future, but not on the day of or the day after the administration of the instrument. This expectation could be important or not important. Participants were instructed not to write down the same event twice. Also in the 3 FET variations, "minimal instructions" were used, that is, participants were not explicitly asked to come up with a specific expectation but were merely asked "Can you write down an expectation that the word X makes you think of?" No examples of correct or incorrect responses were given, and no practice items were provided. Participants were given 60 seconds per cue word to write down an expectation.

The FET-t consisted of 6 positive and 6 negative emotional cue words (eg, happy or sad)[22] (see Supplemental Appendix 1). FET-i and FET-p each included 9 cue words (see Table I for FET-i and see Supplemental Appendix 1 for FET-p). The instructions were identical to those of the general FET, but the participants were explicitly asked to write down expectations concerning itch and pain.

Coding of AMT and FET

Once a participant completed a version of the AMT or FET (itch, pain, traditional), they were instructed, in line with the procedure used by Debeer et al,[21] to assign a code to each response according to the following categories: 1 (specific memory/expectation), M (memory of an event that occurred more than once/expectation that will occur more than once), or > (memory/ expectation of an event lasting for >1 day), or to leave the answer blank (no memory/expectation was written down by the participant).

Afterward, the participants' responses to the AMT and FET were coded by a trained researcher using a method corresponding to that of Debeer et al.[21] Memories/ expectations were coded as specific (see "1" in preceding paragraph) when they referred to a particular event that occurred/will occur within the course of 1 day, at a particular time and place (eg, "When I went to the museum last month I wore a wool sweater which was very itchy"). Nonspecific memories/expectations were qualified as either extended (a memory/expectation of a period lasting for >1 day, eg, "Last week I wore a wool sweater for a couple of days"; see ">" in preceding paragraph), categoric (a memory/expectation that summarizes a number or category of events, eg, "Every time I wore a wool sweater when I was a kid it felt so itchy"; see "M" in preceding paragraph), or semantic associates (verbal association with the cue, eg, "Wool sweaters usually itch"). Failure to provide a memory/ expectation was classified as an omission. Finally, a category of nonresponses included all incomplete responses and all responses on which the instructions had not been followed (ie, events mentioned more than once, unrelated to itch/pain, or that occurred on the day of, before, or after the administration of the instrument).

In cases in which a response was not clear to the researcher, the participant's assigned code was used as a guide, unless the researcher considered the answer to be a semantic associate or nonresponse (which the participant was not able to assign), in which case the researcher decided between semantic associate or nonresponse. If specific, categoric, or

extended was the most likely code according to the researcher and this code matched the participant's assigned code, this code was used as the final code. If a participant's assigned code was not one of the researcher's possibilities, another trained researcher performed the coding, and the 2 codes were compared. If there was disagreement between the 2 researchers, a third trained researcher was consulted and a final code was decided on using majority voting. For analysis of the AMT and FET data, the proportion of specific memories/expectations relative to the total number of memories/expectations was calculated for each participant (eg, AMT-i = [No. of specific responses]/9 – [No. of omissions + No. of nonresponses]).[21]

Self-referential Endorsement and Recall Task adapted for itch and pain

The SER[23] was used for assessing valence of memories and expectations of participants. The SER was adapted by our research group for itch and pain (SER-ip) and included 48 cue words (adjectives) presented on a laptop computer. The task included 12 positive and 12 negative adjectives concerning itch, 12 positive and 12 negative adjectives concerning pain, and 8 filler items, administered in randomized order. The cue words used in the SER-ip were collected from itch and pain questionnaires, online patient panels, and input from a group of volunteers with chronic itch and/or pain complaints and several researchers. Four researchers did the final selection of the words. The itch-related cue words were the focus of this study (Table II); the pain-related cue words can be found in Supplemental Appendix 2. Participants were asked to indicate for each word separately, by clicking "yes" or "no" on the computer screen, whether the word described their experience of itch in the past, experience of pain in the past, expectation of itch in the future, or expectation of pain in the future. A practice trial with general words that were not directly related to itch or pain preceded the actual task to ensure that participants understood the instructions.

Table II. Itch cue words for the Self-referential Endorsement and Recall task (SER) adapted for itch and pain.*

Adjective type	Past	Future
Itch-Positive	Acceptable *(acceptabel)*	Brief *(kortdurend)*
	Reduced *(verminderd)*	Cooled *(verkoeld)*
	Manageable *(handelbaar)*	Improved *(verbeterd)*
	Tolerable *(verdraagbaar)*	Relieved *(verlost)*
	Governable *(beheersbaar)*	Calmed *(gekalmeerd)*
	Overcome *(overwonnen)*	Acceptable *(aanvaardbaar)*
Itch-Negative	Annoying *(irritant)*	Uncontrollable *(oncontroleerbaar)*
	Dominating *(allesbeheersend)*	Untameable *(onbedwingbaar)*
	Constraining *(dwingend)*	Unbearable *(ondraaglijk)*
	Maddening *(gekmakend)*	Intense *(intens)*
	Provoking *(treiterend)*	Persistent *(hardnekkig)*
	Tormenting *(kwellend)*	Impelling *(opjagend)*

* Original cue words in Dutch are shown in parantheses.

Session 2

The procedures of the second laboratory visit (session 2) have previously been described[18] and are summarized here.

Placebo and nocebo effects regarding itch stimuli were induced by verbal suggestion, conditioning, or a combination of both procedures, and compared with those from a control group without expectation induction. Itch was induced with an electrical stimulator (Isolated Bipolar Constant Current Stimulator DS5; Digitimer, Welwyn Garden City, United Kingdom) at a 50-Hz frequency with a pulse duration of 100 μs and at continuously increasing current intensity (0.05 mA/s) to a maximum of 5 mA. The intensity of the stimulation for the low-, medium-, and high-intensity stimuli used in the conditioning design was individually determined.

In the learning phase, 18 itch stimuli were applied, of which the intensities depended on the manipulation from the experimental group. Each itch stimulus was preceded by a colored cue (in total, 6 green, 6 yellow, and 6 red cues) presented on a computer screen. In the learning phase of the verbal suggestion group (n = 23), participants were told that different colored cues indicated that the stimulus intensity would be altered: “A green cue will signal a decrease in itch intensity; a red cue, an increase; and a yellow cue, no change in itch intensity.” Regardless of the color of the cue displayed, all itch stimuli were applied at a medium intensity.

In the conditioning group (n = 24), the green, yellow, and red cues were repeatedly paired with low, medium, and high itch stimulus intensities, respectively. In the conditioning with verbal suggestion group (n = 23), the conditioning procedure and the verbal suggestion procedure were combined. In the control group (n = 25), no expectations regarding the itch stimuli were induced, and the cues were shown with itch stimuli randomly applied at low, medium, or high intensity. Subsequently, in the testing phase, 15 stimuli of medium intensity were applied in all groups (preceded by, in total, 5 green, 5 yellow, and 5 red cues), together with the verbal suggestion that corresponded with the verbal suggestion—if any—given in the learning phase (see Bartels et al[16]). For the purpose of the study, that is, to identify possible placebo responders, only the results from the 3 placebo and nocebo induction groups (and not the control group) were used for the analyses.

Statistical Analysis

All analyses were performed using SPSS version 22.0 (SPSS Inc. Chicago, Illinois). AMT-i and FET-i data were available from 78 of 95 participants. Data from 17 participants were unavailable because we started the experiment using the standard AMT and FET instructions[19] but noticed almost no variation in participants' responses (ie, almost all responses were specific). Therefore, we switched to the Minimal Instructions version, which for the AMT-t has been shown to be more sensitive in detecting reduced autobiographical memory specificity in nonclinical individuals than the standard version.[21] SER-ip data from 1 participant were unavailable due to equipment failure.

The proportion of specific answers on the AMT-i and FET-i were calculated. Mean SER-ip scores on endorsement of itch-related words from the 4 categories (positive/negative, past/future) were separately calculated. Assumptions (eg, of normality) regarding the FET-i and SER-ip statistical test results were violated. Nonparametric tests were used because transforming of data did not result in normal distribution.

For placebo and nocebo responding, the means of the NRS itch scores were calculated for the placebo and nocebo effects in the testing phases of the different groups in session 2. The nocebo effect was calculated as the difference between the mean itch NRS scores associated with the 5 red cues and the 5 yellow cues in the testing phase, and the placebo effect was calculated as the difference between the mean itch NRS scores associated with the 5 green cues and the 5 yellow cues in the testing phase (see Bartels et al[16]). Subsequently, the

median placebo and nocebo effect values from the 3 experimental groups (verbal suggestion, conditioning, and verbal suggestion with conditioning) combined were calculated, and placebo and nocebo responders were classified as being at or above median, while the nonresponders fell into the category of below median. This classification system, used separately for the placebo and nocebo effects, created the median-split factor for use in the analyses.

To exploratively investigate the association between memories and expectations with regard to specificity and valence, correlation between the specificity of memories (AMT-i) and the specificity of expectation (FET-i) was determined in all participants, using the Spearman correlation coefficient. Likewise, correlation between the valence (positive/negative) of memories and valence of expectations regarding itch (SER-ip) was determined in all participants, using the Spearman correlation coefficient.

To test the hypothesis that placebo responders (based on median-split analysis) had more specific memories and expectations regarding itch, while nocebo responders (based on median-split analysis) had less specific memories and expectations regarding itch, 2 independent t tests (regarding the AMT-i) and 2 Mann-Whitney U tests (regarding the FET-i) were performed. To test the hypotheses that placebo responders had endorsed more positive memories and expectations regarding itch and that nocebo responders had endorsed more negative memories and expectations regarding itch, 8 Mann-Whitney U tests were performed. For all analyses, the level of significance was set at $p < 0.05$.

RESULTS

Participants

All 95 participants were of Dutch nationality (a mean [SD] age, 22.7 [3.2] years; 77% women). For analysis of AMT and FET, data from 78 participants were available (see Statistical Analysis section). This population was not significantly different from the main sample with regard to age and sex.

Correlations Between Memory and Expectations for Itch

No significant correlations between the proportion of specific memories (AMT-i) and the proportion of specific expectations (FET-i) for itch were found.

Significant correlations were found between the valence of memories and expectations for itch; the positive and negative memories for itch were both significantly correlated with positive ($r_s = 0.422$; $p < 0.001$) and negative ($r_s = 0.483$; $p < 0.001$) expectations, respectively, for itch. This finding suggests that participants who endorsed more positive memories also endorsed more positive expectations, while those endorsing more negative memories also endorsed more negative expectations.

Specificity of Itch Memories and Expectations in Relation to the Placebo and Nocebo Effects

The mean (SD) proportions of specific memories (AMT-i) and expectations (FET-i) for the placebo and nocebo effects are shown in Table III. An independent samples t test showed that the mean (SD) proportion of specific memories generated in response to itch-related cue words was significantly greater in the placebo responders than in the placebo nonresponders (0.33 [0.15] vs 0.24 [0.15]; t[55] = 2.32; p = 0.024), indicating that participants with more specific itch memories responded more strongly to the placebo itch induction. The difference between the nocebo responders and nonresponders was not significant (t [55] = 0.91; p = 0.365). Mann-Whitney U test did not show a significant difference in FET-i specificity between the placebo responders and nonresponders (U = 372,500, z = –.534, p = .593) or between the nocebo responders and nonresponders (U = 351,000, z = –.910, p = .363).

Valence of Itch Memories and Expectations in Relation to the Placebo and Nocebo Effects

The mean (SD) values of the valence of memories and expectations regarding itch, as measured with the SER-ip, related to the placebo and nocebo effects are shown in Table IV. A Mann-Whitney U test showed significantly fewer negative itch-related expected events in the future in the placebo responders than in the placebo nonresponders (0.97 [1.48] vs 1.33 [1.11]; U = 450.50; z = -1.992; p = 0.046), indicating that participants with less negative itch expectations responded more strongly to the placebo itch induction. No significant differences were found between placebo responders and nonresponders with regard to itch-related negative memories (U = 583.00; z = –0.330; p = 0.742), positive memories (U = 603.00; z = –0.092; p = 0.927), or positive expectations (U = 588.00; z = –0.270; p = 0.788). In nocebo responders and nonresponders, no significant differences were found with regard to itch-related negative memories (U = 581.50; z = –0.371; p = 0.711), negative expectations (U =

527.00; z = –.063; p = 0.288), positive memories (U = 537.00; z = –0.926; p = 0.355), or positive expectations (U = 544.50; z = –0.813; p = 0.416).

Table III. Proportions* of specific memories and expectations for the placebo and nocebo effect, as measured using the adapted Autobiographical Memory Test for itch (AMT-i) and the adapted Future Event Task for itch (FET-i). Data are given as mean (SD).

	Placebo †		Nocebo †		
Task	responders (n=31)	nonresponders (n=26)	responders (n=31)	nonresponders (n=26)	All participants ‡
AMT-i	0.33 (0.15)	0.24 (0.15)	0.30 (0.15)	0.27 (0.17)	0.29 (0.17)
FET-i	0.10 (0.15)	0.12 (0.17)	0.12 (0.16)	0.10 (0.16)	0.10 (0.15)

∗Theoretical range, 0-1. n Values are based on median split.

†Includes participants in the different placebo and nocebo inductions/conditions (ie, the verbal suggestion, conditioning, and conditioning with verbal suggestion groups; the control group was excluded from data analysis).

‡AMT-i, n = 78; FET-i, n = 77; includes the control group.

Table IV. Valence of memories and expectations for the placebo and nocebo effects on the itch as measured with the adapted Self-referential Endorsement and Recall task. Data are given as mean (SD) number.

Type/subtask	Placebo † responders (n=37)	nonresponders (n=33)	Nocebo ‡ responders (n=35)	nonresponders (n=35)	All participants§ (n=94)
Positive					
memories	4.54 (1.79)	4.76 (1.35)	4.54 (1.520	4.74 (1.67)	4.61 (1.53)
expectations	3.46 (1.73)	3.30 (1.31)	3.54 (1.69)	3.23 (1.37)	3.23 (1.53)
Negative					
memories	2.84 (1,59)	2.73 (1.42)	2.82 (1.56)	2.74 (1.46)	2.73 (1.58)
expectations	0.97 (1.48)	1.33 (1.11)	0.94 (1.14)	1.34 (1.47)	1.13 (1.33)

†Placebo responders and nonresponders, n = 37 and 33, respectively, based on median split. Includes participants in the different placebo and nocebo inductions/conditions (ie, the verbal suggestion, conditioning, and conditioning with verbal suggestion groups; the control group was excluded from data analysis).

‡Nocebo responders and nonresponders, n = 35 and 35, respectively, based on median split. Includes participants in the different placebo and nocebo inductions/conditions (ie, the verbal suggestion,

conditioning, and conditioning with verbal suggestion groups; the control group was excluded from data analysis).
§Includes the control group.

DISCUSSION

The findings from the present study suggest that healthy participants' cognitive schemas regarding specificity and valence of memories and expectations for itch are related to placebo responding on itch. More specifically, when investigating the cognitive schemas prior to the induction of placebo and nocebo effects, the placebo responders displayed more specific memories of itch-related events and endorsed fewer negative itch-related expectations for the future than did the placebo nonresponders. In nocebo responders, no significant results were found with regard to specificity and valence of cognitive schemas. Specificity of memories did not seem to be associated with the specificity of expectations, but the valence of memories and expectations were significantly correlated for both negative and positive valenced cognitive schemas. Overall, the findings from the present study suggest for the first time that cognitive memory and expectations tasks may be explored as possible relevant predictors of placebo responses.

The finding concerning specificity of memories and expectations, that is, that placebo responders had previously generated more specific itch-related memories than did nonresponders, is in line with findings from studies on autobiographical memories in relation to psychopathology that indicated that a generalized autobiographic memory, that is, reduced specificity of memories, is related to negative outcomes such as depression and trauma-related psychopathology[12] and difficulties with problem solving.[13] The tendency to be more specific in memory consolidation might be beneficial for the integration of new information, such as learning placebo expectations in the present study. It has also been proposed that reduced autobiographical memory can result from preliminary stopping of the search for a specific memory prior to the retrieval of the specific memory, due to mechanisms such as rumination, avoidance, or reduced executive control.[12] The imagination of future events is sought to occur through the same hierarchical memory system.[24] Moreover, more specific memories have been shown to be related to a better ability to imagine the future[22,25] and thus possibly also imagining expectations regarding a certain treatment. This finding was however

not supported by the associations between specificity of memories on itch and specificity of expectations on itch, which were not significantly associated in our study. In contrast to retrieving itch-related specific memories, participants in our study experienced difficulties in coming up with (specific) expectations for itch, as reflected by the relatively low FET-i scores, which might also explain the lack of the association between itch-related memories and expectations. Finally, no significant differences in specificity of memories or expectations for itch were found between nocebo responders and nonresponders. This finding could be explained by the fact that nocebo effects are easier to induce than are placebo effects, for instance by only 1 verbal suggestion,[26] and may therefore be less sensitive to previous experiences and resulting expectations regarding itch.

The finding concerning valence of memories and expectations, that is, that placebo responders had endorsed fewer negative (but not more positive) itch-related events in the future than did nonresponders, is in line with those from the large body of research that shows that expectations mediate placebo responses.[1] It is also consistent with findings from related studies showing that, compared with healthy controls, patients with chronic pain and depressed patients endorse more negative illness-related words.[23,27] Moreover, it extends this knowledge by showing that not only particular expectations regarding the (placebo) treatment, but also itch-related expectations irrespective of a treatment, may affect placebo itch responding. The link between these generic itch memories and expectations is underlined by the present findings of significant associations between endorsement of more positive and negative memories and expectations, respectively. However, we did not find significant differences in the endorsement of itch-related events in the past between the placebo responders and nonresponders. This finding is in contrast to those from previous studies showing that previous experiences with a certain treatment[14–16] or previous experience with a stimulus[17] can alter placebo responding. An explanation for this could be that the current tasks were conducted in healthy participants whereby we had purposely excluded people with any past (or current) experiences with chronic itch. Furthermore, no significant differences were found between nocebo responders and nonresponders with regard to valence of memories and expectations for itch, which may also be related to nocebo effects being less sensitive to previous experiences and resulting in expectations.

The present study had some limitations. First, participants had difficulties to come up with future expectations regarding itch on the FET. This difficulty may have limited the variability in scores and could explain the lack of findings with regard to this task. Second, minimal instructions were used for the AMT and FET to achieve more variability in the answers of healthy participants. Although previous studies in healthy participants have shown greater variability in specific and general answers and a relationship to depressive symptomatology,[21,28] one cannot exclude that participants came up with more general responses because they did not understand the task due to the limited instructions rather than due to participants' generalized retrieval style. Finally, as the present study was conducted in a nonclinical homogeneous sample, the conclusions cannot be generalized to the general population or to clinical samples, which should be assessed in future research. Moreover, several studies regarding memory specificity have shown that the mechanisms underlying the retrieval of specific memories might differ between patients and healthy participants.[29,30] Therefore it is not yet clear whether and how specificity and valence of memories and expectations regarding itch affect learning of placebo and nocebo itch responding in clinical groups, and patients with chronic itch in particular, which could be addressed in future studies.

This research suggests a relationship between cognitive schemas for memories and expectations regarding itch and placebo responding on itch. It suggests that investigating specificity and valence of memories and expectations seems useful for obtaining insight into the individual differences in placebo responses to further identify possible placebo responders. In the long term, these findings could be useful for identifying patients who will benefit most from the placebo components of a treatment.

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REFERENCES

1. Benedetti F. Mechanisms of placebo and placebo-related effects across diseases. Annu Rev Pharmacol. 2008;48:33–60.
2. Flaten MA, Aslaksen PM, Finset A, et al. Cognitive and emotional factors in placebo analgesia. J Psychosom Res. 2006;61:81–89.
3. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: Recent advances and current thought. Annu Rev Psychol. 2008;59:565–590.
4. Wager TD, Atlas LY, Leotti LA, Rilling JK. Predicting individual differences in placebo analgesia: contributions of brain activity during anticipation and pain experience. J Neurosci. 2011;31:439–452.
5. Stein N, Sprenger C, Scholz J, et al. White matter integrity of the descending pain modulatory system is associated with interindividual differences in placebo analgesia. Pain. 2012;153:2210–2217.
6. Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: Psychological and neurobiological mechanisms. Pain. 2013;154:511–514.
7. Geers AL, Helfer SG, Kosbab K, et al. Reconsidering the role of personality in placebo effects: dispositional optimism, situational expectations, and the placebo response. J Psychosom Res. 2005;58:121–127.
8. Geers AL, Kosbab K, Helfer SG, et al. Further evidence for individual differences in placebo responding: an interactionist perspective. J Psychosom Res. 2007;62:563–570.
10. Webster RK, Weinman J, Rubin GJ. A systematic review of factors that contribute to nocebo effects. Health Psychol. 2016;35:1334–1355.
11. Hall KT, Lembo AJ, Kirsch I, et al. Catechol-O-methyltransferase val158met polymorphism predicts placebo effect in irritable bowel syndrome. PLoS One. 2012;7:e48135.
12. Bartels DJ, van Laarhoven AI, van de Kerkhof PC, Evers AW. Placebo and nocebo effects on itch: effects, mechanisms, and predictors. Eur J Pain. 2016;20:8–13.
13. Williams JM, Barnhofer T, Crane C, et al. Autobiographical memory specificity and emotional disorder. Psychol Bull. 2007;133:122–148.
14. Goddard L, Dritschel B, Burton A. Role of autobiographical memory in social problem solving and depression. J Abnormal Psychol. 1996;105:609–616.
15. Colloca L, Benedetti F. How prior experience shapes placebo analgesia. Pain. 2006;124:126–133.
16. Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. Pain. 2008;136:211–218.
17. Bartels DJ, van Laarhoven AI, Haverkamp EA, et al. Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. PLoS One. 2014;9:e91727.
18. Geers AL, Fowler SL, Wellman JA, et al. Prior experience with a pain stimulus as a predictor of placebo analgesia. J Behav Med. 2015;38:136–142.
19. Kaptchuk TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. Bmj. 2008;336: 999–1003.
20. Williams JM, Broadbent K. Autobiographical memory in suicide attempters. J Abnormal Psychol. 1986;95:144–149.
21. Raes F, Hermans D, de Decker A, et al. Autobiographical memory specificity and affect regulation: an experimental approach. Emotion. 2003;3:201–206.
22. Debeer E, Hermans D, Raes F. Associations between components of rumination and autobiographical memory specificity as measured by a Minimal Instructions Auto-biographical Memory Test. Memory. 2009;17:892–903.
23. Williams JM, Ellis NC, Tyers C, et al. The specificity of autobiographical memory and imageability of the future. Mem Cognit. 1996;24:116–125.
24. Pincus T, Pearce S, McClelland A, Isenberg D. Endorsement and memory bias of self-referential pain stimuli in depressed pain patients. Br J Clin Psychol. 1995;34:267–277.
25. Anderson RJ, Dewhurst SA. Remembering the past and imagining the future: differences in event specificity of spontaneously generated thought. Memory. 2009;17:367–373.
26. Jing HG, Madore KP, Schacter DL. Worrying about the future: An episodic specificity induction impacts problem solving, reappraisal, and well-being. J Exp Psychol Gen. 2016; 145:402–418.

27. van Laarhoven AI, Vogelaar ML, Wilder-Smith OH, et al. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain. 2011;152:1486–1494.

28. Denton FJ, Sharpe L, Schrieber L. Cognitive bias in systemic lupus erythematosus. Eur J Pain. 2005;9:5–14.

29. Raes F, Hermans D, Williams JM, Eelen P. A sentence completion procedure as an alternative to the Autobiographical Memory Test for assessing overgeneral memory in non-clinical populations. Memory. 2007;15:495–507.

30. Watkins ER, Ramponi C, Barnard PJ. Reducing specificity of autobiographical memory in nonclinical participants: The role of rumination and schematic models. Cogn Emot. 2006;20:328–350.

31. Raes F, Watkins ER, Williams JM, Hermans D. Non-ruminative processing reduces overgeneral autobiographical memory retrieval in students. Behav Res Ther. 2008;46: 748–756.

Supplemetary Materials Chapter 6

Appendix 1. Cue words for the traditional version of the AMT and FET

AMT	FET
Happy *(gelukkig)*	Laughing *(lachen)*
Interest *(belangstellend)*	Gift *(cadeau)*
Successful *(succesvol)*	Relaxed *(ontspannen)*
Safe *(veilig)*	Compliment *(compliment)*
Surprised *(verrast)*	Enthusiastic *(enthousiast)*
Proud *(trots)*	Helpful *(behulpzaam)*
Sad *(verdrietig)*	Crying *(huilen)*
Angry *(boos)*	(Being) late *(Laat (zijn))*
Clumsy *(onhandig)*	Fight *(ruzie)*
Hurt *(gekwetst)*	Failing *(fallen)*
Lonely *(eenzaam)*	Nervous *(zenuwachtig)*
Guilty *(schuldig)*	Disappointed *(teleurgesteld)*

Cue words of the traditional version of the Autobiographical Memory Task (AMT-t) and the Future Event Task (FET-t). The cue words translated to English and the original cue words used in Dutch are displayed.

Appendix 2. Pain cue words for the SER

	Past	Future
Pain Positive adjectives	Tolerable *(tolerabel)*	Bearable *(draaglijk)*
	Decreased *(afgenomen)*	Controllable *(controleerbaar)*
	Manageable *(hanteerbaar)*	Maintainable *(houdbaar)*
	Temporary *(voorbijgaand)*	Eased *(verzacht)*
	Cured *(genezen)*	Tamed *(bedwongen)*
	Healed *(geheeld)*	Eased *(verlicht)*
Pain Negative adjectives	Overwhelming *(overweldigend)*	Burdening *(belastend)*
	Penetrating *(doordringend)*	Merciless *(genadeloos)*
	Untenable *(onhoudbaar)*	Debilitating *(slopend)*
	Nagging *(zeurend)*	Heavy *(hevig)*
	Ungovernable *(onbeheersbaar)*	Continuous *(aanhoudend)*
	Exhausting *(afmattend)*	Disturbing *(verontrustend)*

Pain cue words of the Self-referential Endorsement and Recall task (SER) adapted for itch and pain. The cue words translated to English and the original cue words used in Dutch are displayed

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.

References

1. Benedetti F. Mechanisms of placebo and placebo-related effects across diseases. Annu Rev Pharmacol. 2008;48:33-60.
2. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: Recent advances and current thought. Annu Rev Psychol. 2008;59:565-90.
3. Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. Psychosom Med. 2011;73(7):598-603.
4. Darragh M, Chang JW, Booth RJ, Consedine NS. The placebo effect in inflammatory skin reactions: The influence of verbal suggestion on itch and weal size. Journal of psychosomatic research. 2015;78(5):489-94.
5. Meeuwis SH, van Middendorp H, van Laarhoven AIM, Veldhuijzen DS, Lavrijsen APM, Evers AWM. Effects of Open- and Closed-Label Nocebo and Placebo Suggestions on Itch and Itch Expectations. Front Psychiatry. 2019;10:436.
6. Meeuwis SH, van Middendorp H, Veldhuijzen DS, van Laarhoven AIM, De Houwer J, Lavrijsen APM, et al. Placebo Effects of Open-label Verbal Suggestions on Itch. Acta Derm Venereol. 2018;98(2):268-74.
7. van Laarhoven AI, Vogelaar ML, Wilder-Smith OH, van Riel PL, van de Kerkhof PC, Kraaimaat FW, et al. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain. 2011;152(7):1486-94.
8. Skvortsova A, Veldhuijzen DS, Van Middendorp H, Van den Bergh O, Evers AWM. Enhancing Placebo Effects in Somatic Symptoms Through Oxytocin. Psychosom Med. 2018;80(4):353-60.
9. Peerdeman KJ, van Laarhoven AI, Donders AR, Hopman MT, Peters ML, Evers AW. Inducing Expectations for Health: Effects of Verbal Suggestion and Imagery on Pain, Itch, and Fatigue as Indicators of Physical Sensitivity. PLoS One. 2015;10(10):e0139563.
10. Scholz O, Hermanns N. Illness behavior and cognitions influence the perception of itching of patients suffering from atopic dermatitis. Z Klin Psychol. 1994;23:127-35.
11. Schut C, Radel A, Frey L, Gieler U, Kupfer J. Role of personality and expectations for itch and scratching induced by audiovisual itch stimuli. European journal of pain. 2016;20(1):14-8.
12. Schut C, Grossman S, Gieler U, Kupfer J, Yosipovitch G. Contagious itch: what we know and what we would like to know. Frontiers in human neuroscience. 2015;9:57.
13. Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. Pain. 2008;136(1-2):211-8.
14. Brascher AK, Witthoft M. Nocebo hyperalgesia induced by implicit conditioning. J Behav Ther Exp Psychiatry. 2019;64:106-12.
15. Martin-Pichora AL, Mankovsky-Arnold TD, Katz J. Implicit versus explicit associative learning and experimentally induced placebo hypoalgesia. J Pain Res. 2011;4:67-77.
16. Jensen KB, Kaptchuk TJ, Kirsch I, Raicek J, Lindstrom KM, Berna C, et al. Nonconscious activation of placebo and nocebo pain responses. Proc Natl Acad Sci U S A. 2012;109(39):15959-64.
17. Jensen K, Kirsch I, Odmalm S, Kaptchuk TJ, Ingvar M. Classical conditioning of analgesic and hyperalgesic pain responses without conscious awareness. P Natl Acad Sci USA. 2015;112(25):7863-7.
18. Voudouris NJ, Peck CL, Coleman G. The role of conditioning and verbal expectancy in the placebo response. Pain. 1990;43(1):121-8.
19. Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. J Neurosci. 1999;19(1):484-94.
20. Kirsch I, Lynn SJ, Vigorito M, Miller RR. The role of cognition in classical and operant conditioning. J Clin Psychol. 2004;60(4):369-92.
21. van de Sand MF, Menz MM, Sprenger C, Buchel C. Nocebo-induced modulation of cerebral itch processing - An fMRI study. Neuroimage. 2018;166:209-18.
22. Napadow V, Li A, Loggia ML, Kim J, Mawla I, Desbordes G, et al. The imagined itch: brain circuitry supporting nocebo-induced itch in atopic dermatitis patients. Allergy. 2015;70(11):1485-92.
23. Vase L, Riley JL, 3rd, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. Pain. 2002;99(3):443-52.

24. Klinger R, Soost S, Flor H, Worm M. Classical conditioning and expectancy in placebo hypoalgesia: a randomized controlled study in patients with atopic dermatitis and persons with healthy skin. Pain. 2007;128(1-2):31-9.
25. Peerdeman KJ, van Laarhoven AI, Peters ML, Evers AW. An Integrative Review of the Influence of Expectancies on Pain. Front Psychol. 2016;7:1270.
26. Atlas LY, Wager TD. How expectations shape pain. Neuroscience Letters. 2012;520(2):140-8.
27. Crichton F, Petrie KJ. Accentuate the positive: Counteracting psychogenic responses to media health messages in the age of the Internet. Journal of psychosomatic research. 2015;79(3):185-9.
28. Kerkhof I, Vansteenwegen D, Baeyens F, Hermans D. Counterconditioning. Experimental psychology. 2015.
29. Koban L, Kusko D, Wager TD. Generalization of learned pain modulation depends on explicit learning. Acta Psychol (Amst). 2018;184:75-84.
30. Liu C, Chen L, Yu R. Category-based generalization of placebo and nocebo effects. Acta Psychol (Amst). 2019;199:102894.
31. Horing B, Weimer K, Muth ER, Enck P. Prediction of placebo responses: a systematic review of the literature. Front Psychol. 2014;5:1079.
32. Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: Psychological and neurobiological mechanisms. Pain. 2013;154(4):511-4.
33. Ogden J, Zoukas S. Generating physical symptoms from visual cues: An experimental study. Psychology, health & medicine. 2009;14(6):695-704.
34. Schut C, Bosbach S, Gieler U, Kupfer J. Personality traits, depression and itch in patients with atopic dermatitis in an experimental setting: a regression analysis. Acta Derm Venereol. 2014;94(1):20-5.
35. Holle H, Warne K, Seth AK, Critchley HD, Ward J. Neural basis of contagious itch and why some people are more prone to it. Proc Natl Acad Sci U S A. 2012;109(48):19816-21.
36. Weimer K, Colloca L, Enck P. Age and sex as moderators of the placebo response - an evaluation of systematic reviews and meta-analyses across medicine. Gerontology. 2015;61(2):97-108.
37. Zhou L, Wei H, Zhang H, Li X, Bo C, Wan L, et al. The Influence of Expectancy Level and Personal Characteristics on Placebo Effects: Psychological Underpinnings. Front Psychiatry. 2019;10:20.
38. Colagiuri B, Schenk LA, Kessler MD, Dorsey SG, Colloca L. The placebo effect: From concepts to genes. Neuroscience. 2015;307:171-90.
39. Hall KT, Loscalzo J, Kaptchuk TJ. Genetics and the placebo effect: the placebome. Trends Mol Med. 2015;21(5):285-94.
40. Wendt L, Albring A, Benson S, Engler H, Engler A, Hinney A, et al. Catechol-O-methyltransferase Val158Met polymorphism is associated with somatosensory amplification and nocebo responses. PLoS One. 2014;9(9):e107665.
41. Williams JM, Ellis NC, Tyers C, Healy H, Rose G, MacLeod AK. The specificity of autobiographical memory and imageability of the future. Memory & cognition. 1996;24(1):116-25.
42. Williams JM, Broadbent K. Autobiographical memory in suicide attempters. Journal of abnormal psychology. 1986;95(2):144-9.
43. Pincus T, Pearce S, McClelland A, Isenberg D. Endorsement and memory bias of self-referential pain stimuli in depressed pain patients. The British journal of clinical psychology / the British Psychological Society. 1995;34 (Pt 2):267-77.
44. Williams JM, Barnhofer T, Crane C, Herman D, Raes F, Watkins E, et al. Autobiographical memory specificity and emotional disorder. Psychol Bull. 2007;133(1):122-48.
45. Goddard L, Dritschel B, Burton A. Role of autobiographical memory in social problem solving and depression. Journal of abnormal psychology. 1996;105(4):609-16.
46. van Laarhoven AIM, Marker JB, Elberling J, Yosipovitch G, Arendt-Nielsen L, Andersen HH. Itch sensitization? A systematic review of studies using quantitative sensory testing in patients with chronic itch. Pain. 2019;160(12):2661-78.
47. Ikoma A, Steinhoff M, Stander S, Yosipovitch G, Schmelz M. The neurobiology of itch. Nat Rev Neurosci. 2006;7(7):535-47.
48. Forsberg JT, Martinussen M, Flaten MA. The Placebo Analgesic Effect in Healthy Individuals and Patients: A Meta-Analysis. Psychosom Med. 2017;79(4):388-94.

49. Hyland ME. Motivation and placebos: do different mechanisms occur in different contexts? Philos Trans R Soc Lond B Biol Sci. 2011;366(1572):1828-37.
50. Lee HF, Hsieh JC, Lu CL, Yeh TC, Tu CH, Cheng CM, et al. Enhanced affect/cognition-related brain responses during visceral placebo analgesia in irritable bowel syndrome patients. Pain. 2012;153(6):1301-10.
51. Blythe JS, Peerdeman KJ, Veldhuijzen DS, van Laarhoven AIM, Evers AWM. Placebo and nocebo effects on itch: a review of experimental methods. Itch. 2019;4(3):e27.
52. Weisshaar E, Szepietowski JC, Darsow U, Misery L, Wallengren J, Mettang T, et al. European guideline on chronic pruritus. Acta Derm Venereol. 2012;92(5):563-81.
53. Mochizuki H, Inui K, Tanabe HC, Akiyama LF, Otsuru N, Yamashiro K, et al. Time course of activity in itch-related brain regions: a combined MEG-fMRI study. J Neurophysiol. 2009;102(5):2657-66.
54. Mochizuki H, Lavery MJ, Nattkemper LA, Albornoz C, Valdes Rodriguez R, Stull C, et al. Impact of acute stress on itch sensation and scratching behaviour in patients with atopic dermatitis and healthy controls. Br J Dermatol. 2019;180(4):821-7.
55. McSweeney FK, Murphy ES. Sensitization and habituation regulate reinforcer effectiveness. Neurobiol Learn Mem. 2009;92(2):189-98.
56. Savin JA. How should we define itching? J Am Acad Dermatol. 1998;39(2 Pt 1):268-9.
57. Hrobjartsson A, Kaptchuk TJ, Miller FG. Placebo effect studies are susceptible to response bias and to other types of biases. Journal of clinical epidemiology. 2011;64(11):1223-9.
58. Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. Nat Rev Neurosci. 2015;16(7):403-18.
59. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, et al. Placebo-induced changes in FMRI in the anticipation and experience of pain. Science. 2004;303(5661):1162-7.
60. Babel P. Classical Conditioning as a Distinct Mechanism of Placebo Effects. Front Psychiatry. 2019;10:449.
61. Colloca L, Miller FG. How placebo responses are formed: a learning perspective. Philos Trans R Soc Lond B Biol Sci. 2011;366(1572):1859-69.
62. Okusogu C, Colloca L. Placebo hypoalgesia: above and beyond expectancy and conditioning. Curr Opin Behav Sci. 2019;26:75-81.
63. Ader R, Mercurio MG, Walton J, James D, Davis M, Ojha V, et al. Conditioned Pharmacotherapeutic Effects: A Preliminary Study. Psychosom Med. 2010;72(2):192-7.
64. Colloca L, Benedetti F. Placebo analgesia induced by social observational learning. Pain. 2009;144(1-2):28-34.
65. Vogtle E, Barke A, Kroner-Herwig B. Nocebo hyperalgesia induced by social observational learning. Pain. 2013;154(8):1427-33.
66. Tu Y, Park J, Ahlfors SP, Khan S, Egorova N, Lang C, et al. A neural mechanism of direct and observational conditioning for placebo and nocebo responses. Neuroimage. 2019;184:954-63.
67. Papoiu AD, Wang H, Coghill RC, Chan YH, Yosipovitch G. Contagious itch in humans: a study of visual 'transmission' of itch in atopic dermatitis and healthy subjects. Br J Dermatol. 2011;164(6):1299-303.
68. Andersen HH, Elberling J, Arendt-Nielsen L. Human surrogate models of histaminergic and non-histaminergic itch. Acta Derm Venereol. 2015;95(7):771-7.
69. Yosipovitch G, Papoiu AD. What causes itch in atopic dermatitis? Current allergy and asthma reports. 2008;8(4):306-11.
70. Verhoeven EW, de Klerk S, Kraaimaat FW, van de Kerkhof PC, de Jong EM, Evers AW. Biopsychosocial mechanisms of chronic itch in patients with skin diseases: a review. Acta Derm Venereol. 2008;88(3):211-8.
71. Colloca L, Wang Y, Martinez PE, Chang YC, Ryan KA, Hodgkinson C, et al. OPRM1 rs1799971, COMT rs4680, and FAAH rs324420 genes interact with placebo procedures to induce hypoalgesia. Pain. 2019;160(8):1824-34.
72. Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK. Neurobiological mechanisms of the placebo effect. J Neurosci. 2005;25(45):10390-402.
73. Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: Unraveling the mechanisms of the nocebo effect. Neuroscience. 2007;147(2):260-71.

74. Atlas LY, Wager TD. A meta-analysis of brain mechanisms of placebo analgesia: consistent findings and unanswered questions. Handbook of experimental pharmacology. 2014;225:37-69.
75. Mochizuki H, Baumgartner U, Kamping S, Ruttorf M, Schad LR, Flor H, et al. Cortico-subcortical activation patterns for itch and pain imagery. Pain. 2013;154(10):1989-98.
76. Schut C, Mochizuki H, Grossman SK, Lin AC, Conklin CJ, Mohamed FB, et al. Brain Processing of Contagious Itch in Patients with Atopic Dermatitis. Front Psychol. 2017;8:1267.
77. Blease C, Colloca L, Kaptchuk TJ. Are open-Label Placebos Ethical? Informed Consent and Ethical Equivocations. Bioethics. 2016;30(6):407-14.
78. Meeuwis SH, van Middendorp H, Pacheco-Lopez G, Ninaber MK, Lavrijsen APM, van der Wee N, et al. Antipruritic Placebo Effects by Conditioning H1-antihistamine. Psychosom Med. 2019;81(9):841-50.
79. Evers AWM, Colloca L, Blease C, Annoni M, Atlas LY, Benedetti F, et al. Implications of Placebo and Nocebo Effects for Clinical Practice: Expert Consensus. Psychotherapy and psychosomatics. 2018;87(4):204-10.
80. Stewart-Williams S, Podd J. The placebo effect: dissolving the expectancy versus conditioning debate. Psychological bulletin. 2004;130(2):324-40.
81. Rief W, Bingel U, Schedlowski M, Enck P. Mechanisms involved in placebo and nocebo responses and implications for drug trials. Clin Pharmacol Ther. 2011;90(5):722-6.
82. Barnes K, Faasse K, Geers AL, Helfer SG, Sharpe L, Colloca L, et al. Can Positive Framing Reduce Nocebo Side Effects? Current Evidence and Recommendation for Future Research. Front Pharmacol. 2019;10:167.
83. Pan Y, Kinitz T, Stapic M, Nestoriuc Y. Minimizing Drug Adverse Events by Informing About the Nocebo Effect-An Experimental Study. Front Psychiatry. 2019;10:504.
84. Hauser W, Hansen E, Enck P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. Dtsch Arztebl Int. 2012;109(26):459-65.
85. Zunhammer M, Ploner M, Engelbrecht C, Bock J, Kessner SS, Bingel U. The effects of treatment failure generalize across different routes of drug administration. Sci Transl Med. 2017;9(393).
86. Carlino E, Vase L, Piedimonte A. Mechanisms of Placebo and Nocebo. Placebos and Nocebos in Headaches: Springer; 2019. p. 43-55.

Samenvatting (Dutch summary)

Placebo- en nocebo-effecten zijn respectievelijk positieve en negatieve behandeleffecten, welke geen verband houden met het behandelingsmechanisme, maar welke kunnen worden toegeschreven aan de verwachtingen van de patiënt. Van placebo- en nocebo-effecten is bekend dat ze een rol spelen bij de behandeleffecten van verschillende symptomen en aandoeningen, vooral op het gebied van pijn. Het primaire doel van het huidige proefschrift was om de kennis van placebo- en nocebo-effecten op het gebied van jeuk te vergroten.

In **Hoofdstuk 2** hebben we een overzicht gegeven van de empirische literatuur over placebo- en nocebo-effecten bij jeuk en de voorspellers van placebo- en nocebo-effecten bij jeuk met betrekking tot individuele kenmerken. Daarnaast werden deze bevindingen vergeleken met wat bekend is op het gebied van pijn. We lieten zien dat verwachtingsleren via verbale suggestie (het geven van mondelinge of schriftelijke informatie over de uitkomst van een bepaalde placebo of actieve behandeling) en conditionering ((associatief leren van een relatie tussen een geconditioneerde stimulus (bv. de kleur en vorm van een pil) en een ongeconditioneerde stimulus (bv. het actieve bestandsdeel in de pil)) placebo- en nocebo-effecten op jeuk kan induceren. Aansluitend bij bevindingen uit eerder onderzoek bij pijn, bleek dat de combinatie van beide procedures het meest veelbelovend is om placebo- en nocebo-effecten te induceren (zie ook hoofdstuk 3). Daarnaast kan jeuk 'besmettelijk' zijn: als we een ander zien krabben, krijgen we zelf ook jeuk en/of de neiging om te krabben. Verwachtingen lijken hierbij een rol te spelen. Dit fenomeen is karakteristiek voor jeuk en komt niet in dezelfde mate voor bij bijvoorbeeld pijn. Met betrekking tot voorspellers van placebo- en nocebo-effecten op jeuk en besmettelijke jeuk, laat voorlopig bewijs een mogelijke rol zien voor individuele psychologische kenmerken en persoonlijkheidskenmerken die verband houden met negatieve uitkomstverwachtingen, zoals neuroticisme, angst, depressie of piekeren, maar de resultaten zijn gemengd. Tot dusver zijn er geen eenduidige voorspellers voor placebo- en nocebo-effecten ten aanzien van jeuk gevonden.

In **Hoofdstuk 3** hebben we in een experiment de effecten onderzocht van verwachtingsleren via verbale suggestie, conditionering en de combinatie van beiden, voor het induceren van placebo- en nocebo-effecten op elektrisch geïnduceerde jeuk bij gezonde

deelnemers. Deze studie toonde aan dat significante placebo- en nocebo-effecten werden geïnduceerd wanneer de combinatie van conditionering en verbale suggestie werd toegepast in vergelijking met een controleprocedure. Wanneer de conditionering- en verbale suggestieprocedure afzonderlijk toegepast werden, resulteerde dit niet in significante placebo- en nocebo-effecten in vergelijking met de controleprocedure. De resultaten in deze studie zijn vergelijkbaar met onderzoek naar pijn en andere sensaties zoals misselijkheid, welke over het algemeen hebben aangetoond dat de grootste placebo- en nocebo-effecten worden verkregen wanneer verbale suggestie wordt gecombineerd met conditionering. Verder vonden we aanwijzingen dat individuele kenmerken gerelateerd aan negatieve uitkomstverwachtingen, zoals meer zorgen maken, hogere negatieve affectiviteit, minder hoop en minder extraversie, geassocieerd waren met grotere nocebo-responsen voor jeuk, terwijl er slechts één significante correlatie werd gevonden met placebo-effecten, namelijk dat grotere placebo effecten voor jeuk samenhingen met minder hoop.

In **Hoofdstuk 4** hebben we onderzocht of het mogelijk was om eerder ontstane nocebo-effecten op jeuk op te heffen. Daartoe hebben we eerst nocebo-effecten geïnduceerd met betrekking tot elektrisch opgewekte jeuk bij gezonde deelnemers met behulp van conditionering en verbale suggestie. Vervolgens, om de nocebo-effecten te verminderen, werden positieve verwachtingen geïnduceerd door conditionering met verbale suggestie (counterconditionering), terwijl in de controlecondities ofwel werd doorgegaan met induceren van negatieve verwachtingen of een extinctieprocedure (d.w.z. het herhaaldelijk aanbieden van de geconditioneerde stimulus zonder de ongeconditioneerde stimulus) werd toegepast. De resultaten toonden aan dat de counterconditionering de nocebo-effecten op jeuk verminderde in vergelijking met de controlecondities. De jeukscores waren zelfs dusdanig laag, dat het nocebo effect volledig was omgekeerd en er een placebo effect was ontstaan. We vonden ook aanwijzingen dat de verminderde nocebo-effecten met betrekking tot jeuk opgeroepen door elektrische stimulatie generaliseerden naar verminderde jeuk opgeroepen door een andere jeukprikkel, namelijk histamine. Individuele kenmerken bleken niet geassocieerd te zijn met de waargenomen effecten op jeuk. Deze studie laat zien dat leren via counterconditionering in combinatie met verbale suggestie een veelbelovende strategie lijkt om nocebo-effecten ten aanzien van jeuk te verminderen.

In **Hoofdstuk 5** hebben we onderzocht of nocebo-effecten en gecounterconditioneerde nocebo-effecten op elektrisch geïnduceerde jeuk (zie hoofdstuk 4) generaliseren naar krabgedrag. Deze experimentele studie toonde aan dat deelnemers meer krabben wanneer jeukstimuli met een hogere intensiteit worden toegediend dan wanneer jeukstimuli met een lagere intensiteit worden toegediend. Afgezien van enkele indirecte aanwijzingen werden er echter geen significante nocebo-effecten of omgekeerde nocebo-effecten op het krabgedrag van de deelnemers gevonden. Deze bevindingen suggereren dat ondanks het nauwe verband tussen jeuk en krabben, generalisatie van nocebo-effecten van jeuk naar krabben niet noodzakelijk hoeft op te treden. Dit zou onder meer verklaard kunnen worden door de matige intensiteit van de ervaren jeuk of de specificiteit van de verbale suggestie, die enkel gericht was op jeuk; er werd geen aanvullende verbale suggestie met betrekking tot het krabben gegeven.

In **Hoofdstuk 6** hebben we onderzocht wat de rol is van jeuk-gerelateerde herinneringen en verwachtingen die deelnemers hebben - oftewel cognitieve schema's – bij placebo en nocebo effecten op jeuk. Daartoe werden de specificiteit en valentie van herinneringen en verwachtingen over jeuk-gerelateerde gebeurtenissen onderzocht bij gezonde deelnemers. Dit gebeurde voorafgaand aan deelname aan een placebo- en nocebo-experiment ten aanzien van jeuk zoals beschreven in hoofdstuk 3. De resultaten gaven aan dat deelnemers die specifieker waren in hun jeuk-gerelateerde herinneringen en die minder negatieve jeuk-gerelateerde verwachtingen voor de toekomst hadden, vaker placebo-*responders* dan *non-responders* waren, oftewel vaker met jeukvermindering reageerden op de positieve verwachtingsinductie. Er werden geen significante verschillen in cognitieve schema's gevonden tussen de nocebo-*responders* en *non-responders*. Cognitieve schema's van jeuk-gerelateerde herinneringen en verwachtingen kunnen veelbelovend zijn bij het verklaren van interindividuele verschillen op placebo-effecten bij jeuk.

Tot besluit onderstrepen de bevindingen van de studies in dit proefschrift dat placebo- en nocebo-effecten een rol spelen bij jeukbeleving. We vonden dat jeuk zeer ontvankelijk is voor suggesties en dat placebo- en nocebo-effecten op jeuk kunnen worden geïnduceerd door verbale suggestie en conditionering. Hierbij laten onze bevindingen voor het eerst zien dat met name de combinatie van conditionering met verbale suggestie het beste effect bewerkstelligt bij het induceren van zowel placebo- als nocebo-effecten op jeuk. Dit is in

overeenstemming met placebo-onderzoek bij pijn. Bovendien, een nieuwe en tevens veelbelovende bevinding is dat eerder ontstane nocebo-effecten op jeuk weer kunnen worden omgekeerd door middel van counterconditionering. Toekomstig onderzoek kan voortbouwen op de bevindingen van dit proefschrift om onze kennis over placebo- en nocebo-effecten op jeuk verder te vergroten. Deze kennis kan aanknopingspunten bieden om verder te onderzoeken hoe we deze placebo- en nocebo-effecten het beste kunnen maximaliseren respectievelijk minimaliseren, ook in een klinische setting, om uiteindelijk interventies voor patiënten met chronische jeuk te optimaliseren.

Curriculum Vitae

Danielle Bartels werd geboren op 12 maart 1988 te Nijmegen. Zij groeide op in Lomm, een klein dorpje nabij Venlo. Na het behalen van haar vwo-diploma in 2006 aan het Valuas college te Venlo, verhuisde ze naar Nijmegen om Psychologie te studeren aan de Radboud Universiteit. Ze koos voor de richting Klinische Psychologie en behaalde in 2012 haar Masterdiploma. Tijdens haar studietijd liep ze een jaar stage bij Hendriks en Roosenboom te Arnhem. Hier behandelde ze volwassenen met uiteenlopende problematiek zoals stemmings- en angststoornissen en ontwikkelingsproblematiek. Haar Masterscriptie schreef ze over placebo en nocebo effecten bij jeuk op de afdeling Medische Psychologie van het Radboudumc. In 2012 werd Danielle aangesteld als promovenda op de afdeling Medische Psychologie van het Radboudumc. In 2014 volgt ze haar eerste promotor en co-promotor naar de sectie Gezondsheids-, Medische en Neuropsychologie van de Universiteit Leiden, waar ze haar promotieonderzoek voortzette. Haar promotieonderzoek maakte deel uit van de onderzoeksschool Experimentele Psychopathologie (EPP). Haar onderzoek werd gefinancierd door een VIDI beurs van De Nederlandse Organisatie voor Wetenschappelijk Onderzoek en later ook een ERC Consolidator beurs, beide toegekend aan Prof. dr. Andrea Evers. Tijdens haar promotieonderzoek heeft Danielle diverse presentaties verzorgd op nationale en internationale congressen binnen de medische wetenschappen en psychologie. Danielle heeft voor haar onderzoek verschillende prijzen ontvangen zoals de prijs voor beste posterpresentatie op het 2e ARPH (Association for Researchers in Psychology and Health) congres in Enschede (2013), een prijs voor beste artikel van de sectie Gezondsheids-, Medische en Neuropsychologie van de Universiteit Leiden (2016) en een Reisbeurs van de *International Forum for the Study of Itch* (IFSI) voor het presenteren van haar onderzoek op het *9th World Congress on Itch* in Polen (2017). Tijdens haar onderzoek verrichtte Danielle ook onderwijstaken, waaronder het begeleiden van Bachelor- en Masterstudenten Psychologie in het kader van hun (afstudeer)scriptie. Tevens is Danielle aangesteld geweest als docent aan de Universiteit Leiden (2017) en is ze werkzaam geweest als psycholoog bij het Rughuis te Eindhoven, waar ze bijdroeg aan de interdisciplinaire behandeling mensen met chronische rug-, bekken,- en nekklachten (2018). Momenteel is Danielle werkzaam als Docent Toegepaste Psychologie aan de Fontys Hogenscholen te Eindhoven. Ze woont in Eindhoven en is getrouwd met Teun Slot.

Publications

Articles in international peer reviewed journals

Bartels D.J.P., van Laarhoven A.I.M., van de Kerkhof P.C.M., & Evers A.W.M. (2018) Nocebo Effects and Scratching Behaviour on Itch. *Acta dermato-venereologica*. https://doi.org/10.2340/00015555-2979

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Peerdeman, K.J., Laarhoven, A.I.M., **Bartels, D.J.P**., Peters, M.L., & Evers, A.W.M. (2017). Placebo-like analgesia via response imagery. *European Journal of Pain*.

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Book chapters

Evers A.W.M., Peerdeman K.J., **Bartels D.J.P**., & van Laarhoven A.I.M. (2016). Placebo and Nocebo effects on Itch: Methodological and clinical implications. In L. Misery & S. Stander (Eds.) *Pruritus. 2nd edition* (pp. 103-110), *Springer International Publishing.*

Evers, A.W.M., **Bartels, D.J.P**. & van Laarhoven A.I.M. (2014) Placebo and Nocebo Effects in Itch and Pain. In F. Benedetti et al. (eds.), *Placebo* (pp. 205-214) Handbook of Experimental Pharmacology.225, DOI 10.1007/978-3-662-44519-8

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Danielle

[1] ET Canada (2018, 19 november) *Snoop Dogg Gets Star On Hollywood Walk Of Fame | FULL SPEECH* [Videobestand] geraadpleegd op 13-9-2020 van https://www.youtube.com/watch?v=GvpZ2mcUJWc