Placebo and nocebo effects on itch: An experimental approach

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CHAPTER 2

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

MINI REVIEW

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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.

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