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Induction of nocebo and placebo effects on itch and pain by verbal suggestions

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ABSTRACT

Physical complaints, such as pain, can be effectively reduced by placebo effects through induction of positive expectations, or increased by nocebo effects through induction of negative expectations. In the present study, verbally induced nocebo and placebo effects on itch were experimentally investigated for the first time. In part 1, the role of verbal suggestions in inducing nocebo effects on itch and pain was investigated. All subjects received the same somatosensory quantitative sensory testing stimuli, that is, mechanical and electrical stimuli and application of histamine, and verbal suggestions to manipulate expectations regarding the stimuli. The suggestions were designed to produce either high expectations for itch (itch nocebo) or pain (pain nocebo) or low expectations for itch (itch nocebo control) or pain (pain nocebo control). Results showed that high itch and pain expectations resulted in higher levels of itch and pain, respectively. When comparing nocebo effects, induced by verbal suggestions, results were more pronounced for itch than for pain. In part 2, verbal suggestions designed to produce a placebo effect on itch (itch placebo) or pain (pain placebo), or neutral suggestions (itch placebo control and pain placebo control) were given regarding a second application of histamine and compared with the first application applied in part 1. Results of placebo effects only showed a significantly larger decrease in itch in the itch placebo condition than in the pain placebo condition. In conclusion, we showed for the first time that nocebo and possibly placebo responses can be induced on itch by verbal suggestions.

1. Introduction

Placebos can affect a wide variety of subjective, behavioral, and physiological responses, and are effective in, for example, depression, Parkinson's disease, irritable bowel syndrome, and pain [4,18,23,30,40,53]. In contrast to the placebo effect, less attention has been directed to the nocebo effect, which is based on the induction of negative expectations and allows investigation of worsening of complaints [7,11,37,47]. Research into the mechanisms of placebo and nocebo has mainly concentrated on expectation learning processes, involving both verbal suggestions and conditioning [9,16]. These studies generally showed that placebo effects are larger when verbal suggestions were combined with conditioning; nocebo effects were equally effective when verbal suggestions were given alone or in combination with conditioning [11,12,33].

Itch is a major symptom of many chronic skin conditions affecting up to 50% of patients with skin disease in general practice [54]. In both chronic itch and pain, comparable processes of central and peripheral sensitization are thought to play a main role in symptom-worsening. For example, sensitization phenomena of allodynia and hyperalgesia, well known in pain, similarly play a role in itch (alloknesis and hyperknesis) [3,43,45]. Furthermore, in both localized painful and pruritic lesions, levels of nerve growth factor are increased and inflammatory mediators, for example, bradykinin, histamine, and prostaglandins, have an acute sensitization effect on peripheral nociceptors and also provoke itch [25,29]. From a neurophysiological point of view, corresponding brain areas (eg, the primary and secondary somatosensory cortex or anterior cingulated cortex) are activated in pain and itch processing, although the brain area activation patterns and neuronal processing differs [28,48]. In view of the considerable overlap between itch and pain, sensitization processes influenced by expectations

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regarding increase or decrease in physical sensations, as relevant to placebo and nocebo effects, may also similarly influence pain and itch. There is some indirect evidence suggesting a role of nocebo effects in itch. For example, it has been shown that patients with atopic dermatitis react more strongly to histamine when given verbal suggestions for exaggerated skin reactions and itch [44]. Furthermore, the frequency of scratching of uninformed subjects was significantly higher during a lecture about itch than during a neutral lecture [36]. Taking this into account, nocebo and placebo effects induced by verbal suggestions may also be relevant to itch. Investigation of these mechanisms in pruritus may also contribute to validation of concepts of nociception [43], and studying nocebo and placebo effects on different sensations, such as pain and itch, further adds to the knowledge of generic and symptom-specific psychophysiological mechanisms of nocebo and placebo responding. The aim of the present study was to investigate the role of verbal suggestions in nocebo and placebo effects on itch and pain.

2. Methods

Part 1 of this study aimed to explore the role of nocebo effects on itch and pain induced by verbal suggestions manipulating expectations (high/low expectations for itch/pain) regarding various somatosensory stimuli that can evoke itch and pain. In part 2 of this study, subjects were given either suggestions of a decrease in itch or pain, or neutral suggestions regarding a second application of histamine additional to the first application in part 1. The two parts of the study were performed on the same day, with a 15-minute interval in between.

2.1. Part 1: nocebo effects on itch and pain

2.1.1. Participants

One hundred five healthy female subjects aged 18 years and older (mean age 21.8 years, SD = 2.2) were recruited at the university campus of Radboud University, Nijmegen, the Netherlands. Exclusion criteria were severe morbidity (eg, multiple sclerosis, diabetes mellitus, heart or lung diseases), psychiatric disorders (eg, depression), use of pacemaker, use of systemic medication in the previous 24 hours, and chronic itch or pain complaints either currently or in the past. The sample consisted of Dutch (96%) or German (4%) nationalities; all could speak and write Dutch fluently. Of the subjects, 55% had a partner (11% were married or living with their partner), and 69% used oral contraceptives. The protocol was approved by the regional medical ethics committee. On arrival at the test facility, participants were asked to score their current levels of itch and pain on a visual analogue scale (VAS) ranging from 0 (no itch/pain at all) to 10 (worst itch/pain imaginable). Mean levels of itch and pain on the day of testing were 0.2 (SD = 0.6) and 0.3 (SD = 0.6), respectively. Multivariate analyses of variance (MANOVA) analysis showed no significant differences between the experimental conditions (see Section 2.1.3) with regard to age, body mass index, educational level, use of oral contraceptives, and current itch and pain on the day of testing.

2.1.2. General procedure

Self-report questionnaires were sent to the participants 1 week before the experiment. On arrival at the test facility, participants were informed about the study and all participants gave their informed consent prior to the investigation. Participants had earlier been instructed not to drink black tea or coffee 1 hour before testing. Subjects were informed about the study (including parts 1 and 2 of the experiment) by describing the general purpose of the studies in an experimental context of a study investigating sensitivity to somatosensory stimuli. They were not aware that they were being randomly assigned to one of the four experimental conditions (2×2 design with respect to the itch nocebo condition with high expectation, itch nocebo control condition with low expectation, pain nocebo condition with high expectation, and pain nocebo control condition with low expectation) or, subsequently, to one of the placebo conditions (only subjects in the high expectations itch and pain conditions). Subjects received condition-appropriate verbal information about the stimuli to be applied. Somatosensory quantitative sensory testing stimuli [26] were applied in the following order: monofilament stimulation, electrical stimulation, and histamine iontophoresis (see Fig. 1 for a flow diagram of the stimuli). The same stimuli were applied to all subjects, either with a predetermined intensity (mechanical, electrical, and chemical stimulation) or tailored to the subject's threshold (electrical stimulation). For each stimulus and in all experimental conditions, subjects were instructed to rate the perceived levels of itch and pain on a VAS ranging from 0 (no itch/pain) to 10 (the worst itch/pain imaginable). All subjects were tested by the same male experimenter.

2.1.3. Experimental nocebo conditions

Subjects were randomly assigned to one of four nocebo conditions, two for itch and two for pain: itch nocebo condition (high expectation; $n = 36$), itch nocebo control condition (low expectation; $n = 20$), pain nocebo condition (high expectation; $n = 33$), or pain nocebo control condition (low expectation; $n = 16$). All subjects were told that they were participating in a study investigating sensitivity to somatosensory stimuli evoking, for example, itch and pain, and that they were randomized to receive either itch or pain stimuli. The following instructions were given.

2.1.3.1. Itch conditions. Subjects in both itch conditions were told that they would receive itch stimuli. In the *itch nocebo condition*

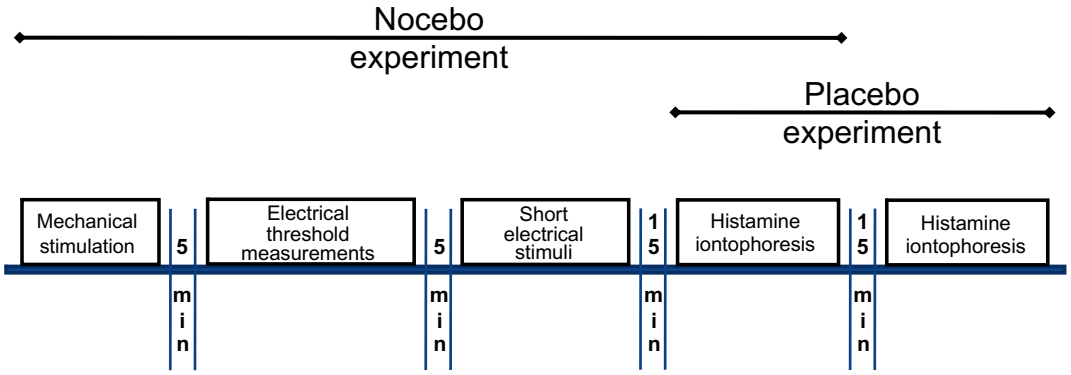

Fig. 1. Flow diagram of the application of stimuli in part 1 (nocebo) and part 2 (placebo) of the study.

(*high expectation*), subjects were told that "95% of healthy people experience itch from these stimuli. Very few, maximally 5%, experience pain," in order to induce high itch expectations. Instructions were briefly repeated ("nearly all healthy people experience itch from these stimuli, while hardly anyone experiences pain") before the somatosensory stimuli were applied. In the *itch nocebo control condition* (*low expectation*), subjects were told that "As few as 5% of healthy people experience itch from these stimuli, and only 5% of healthy people experience pain," in order to induce low itch expectations. In addition, before somatosensory stimuli were applied to subjects in the nocebo control condition, the instructions were briefly repeated: "hardly any healthy people experience itch from these stimuli, and hardly anyone experiences pain." After the instructions were given, subjects in both itch conditions were asked to indicate the levels of itch and pain they expected to feel from the stimuli on a VAS from 0 to 10. As expected, subjects in the *itch nocebo condition* (*high expectation*) expected to feel significantly higher levels of itch ($t = 5.52$, $P < 0.001$) than the subjects in the *itch nocebo control condition* (*low expectation*), while the levels of pain expected by the subjects did not differ between both conditions ($t = 1.22$, $P = 0.21$).

2.1.3.2. Pain conditions. The instructions for the subjects in the *pain nocebo condition* (*high expectation*) and *pain nocebo control condition* (*low expectation*) were the same as for the itch nocebo conditions, except that the word "itch" was replaced by the word "pain," and vice versa. After the instructions, the subjects in both pain conditions were asked to indicate the levels of pain and itch they expected to feel from the stimuli on a VAS from 0 to 10. As expected, subjects in the *pain nocebo condition* (*high expectation*) expected to feel significantly higher levels of pain ($t = 6.16$, $P < 0.000$) than the subjects in the *pain nocebo control condition* (*low expectation*), while the levels of itch expected did not differ between the conditions ($t = 0.73$, $P = 0.47$).

2.1.4. Somatosensory stimuli

All subjects received the same somatosensory stimuli of similar intensity that have previously been validated for inducing itch and/or pain [50,51]. They were asked to report the levels of itch and pain they experienced for each stimulus separately on a VAS ranging from 0 to 10. Interval time in between the stimuli was chosen based on earlier studies showing that mean subjective experiences of itch and pain were adequately diminished after the stimuli interval times [50,51].

2.1.4.1. Mechanical stimulation. Mechanical stimulation was applied by using two Semmes-Weinstein von Frey calibrated monofilaments of 15.0 and 75.0 g. The choice of filaments was based on a previous study of our group investigating when a pricking sensation, which can evoke itch, pain, or both, is perceived [51]. The filaments were applied vertically consecutively for 2 seconds to the nondominant forearm (2 cm distal to the epicondyle of the humerus, C5 dermatome), while avoiding contact with body hair. The interval between the filaments was at least 30 seconds and the interval between mechanical stimulation and electrical stimulation was at least 5 minutes.

2.1.4.2. Electrical stimulation. Cutaneous electrodes were applied to the nondominant forearm, 2 cm distal to the epicondyle of the humerus (C5 dermatome). Electrical stimulation was administered using a constant current nerve stimulator (Pajunk; Geisingen, Germany). The electrical tolerance threshold, a tailored measure, taking into account the subjects' interindividual variability, was defined by "the moment that the sensation becomes unbearable and you want to stop immediately." The electrical tolerance threshold was determined twice by ramping with continuous increasing intensity (about 0.2 mA/s) [50]. The electrical stimulation was applied at 100-Hz frequency with 0.3-ms pulse duration, a stimulus frequency and intensity previously shown to evoke pain as well as itch [27,50,51]. The subjects were asked to report itch and pain scores immediately after the electrical stimulation. Mean VAS scores were calculated. Next, subjects were instructed that they would receive three different electrical stimuli of short duration. Subjects actually received three similar stimuli for 3 seconds at 6.0 mA intensity (100-Hz frequency, 0.3-mA pulse duration). For each electrical stimulus, subjects were asked to score itch and pain on the VAS, and the mean of these VAS scores were calculated. The interval between the threshold measurements and between the three electrical stimuli was at least 30 seconds, and the interval between threshold measurements and the first short electrical stimulus was at least 5 minutes. The interval between electrical stimulation and histamine iontophoresis was at least 15 minutes.

2.1.4.3. Histamine iontophoresis. Histamine was applied by iontophoresis (Chattanooga Group, Hixson, TN, USA). Histamine dihydrochloride (0.5%) was dissolved in a gel of 2% methylcellulose in distilled water and 2.0 mL was placed in an electrode (Chattanooga Ionto Ultra Electrode medium), which was applied to the dominant forearm, 2 cm distal to the lateral epicondyle of the humerus (C5 dermatome). The reference electrode (area: 38.7 cm^2) was applied to the skin on the lateral side of the triceps brachial muscle. Current level was set at 1.0 mA and histamine was delivered for 2.5 min [50]. Histamine iontophoresis is particularly known to induce itch [28], however, it may also induce low levels of pain [3,50,51]. During histamine application, subjects were asked to rate the intensity of itch and pain every 30 seconds. The mean VAS scores during application were calculated.

2.2. Part 2: placebo effects on itch and pain

2.2.1. Participants

The sixty-nine subjects who were randomized to the high-expectation conditions of part 1 (36 subjects of the *itch nocebo condition* [*high expectation*] and 33 subjects of the *pain nocebo condition* [*high expectation*]) also participated in part 2. There were no significant differences in demographics and study characteristics of the subjects participating in this part of the study compared with those in part 1. Mean levels of current itch and pain were 0.1 (SD = 0.3) and 0.3 (SD = 0.7), respectively, on the day of testing. MANOVA analysis showed that there were no significant differences between the experimental placebo conditions (see Section 2.2.3) with regard to age, body mass index, educational level, use of oral contraceptives, and current itch and pain on the day of testing.

2.2.2. General procedure

All participants of part 2 had also participated in part 1, when the 2 parts of the experiment had been introduced within the same experimental context of testing sensitivity to somatosensory stimuli. Subjects from the *itch nocebo condition* (*high expectation*) of part 1 were randomly assigned to either the *itch placebo* or *itch placebo control condition*, and subjects from the *pain nocebo condition* (*high expectation*) of part 1 were randomly assigned to either the *pain placebo* or *pain placebo control condition* (2×2 repeated measures design), while for subjects from the *itch and pain nocebo control conditions* (*low expectation*) of part 1, testing stopped after part 1. Depending on the experimental placebo condition (itch/pain placebo or placebo control) subjects were assigned to, they received verbal information regarding the sensory stimulus they would receive (see Section 2.2.3). Subsequently, histamine was applied for the second time, now to the nondominant forearm, using an

identical procedure as in part 1 (see Fig. 1 for a flow diagram of the stimuli). Subjects were instructed to rate the perceived levels of itch and pain on a VAS ranging from 0 (no itch/pain) to 10 (the worst itch/pain imaginable).

2.2.3. Experimental placebo conditions

The subjects from the *itch nocebo condition* (*high expectation*) of part 1 were randomly assigned to 1 of the 2 experimental conditions for itch placebo: *itch placebo condition* ($n = 20$) and *itch placebo control condition* ($n = 16$), while the subjects from the *pain nocebo condition* (*high expectation*) of part 1 were randomly assigned to 1 of the 2 experimental conditions for pain placebo: *pain placebo condition* ($n = 15$) and *pain placebo control condition* ($n = 18$). The following instructions were given.

2.2.3.1. Itch placebo conditions. In the *itch placebo condition*, subjects received the following suggestions before histamine was applied for the second time: "Now I will apply the same gel to the other forearm, but I added an itch-reducing substance to this gel, which reduces itch in such a way that nearly all healthy people do not experience itch anymore." In the *itch placebo control condition*, subjects received the following suggestions before histamine was applied for the second time: "Now I will apply the same itching gel to the other forearm. Nearly all healthy people experience itch from these stimuli, while hardly anyone experiences pain." The instructions given to the subjects in the placebo control condition, the aim of which was to investigate the effects of repeated application of histamine, corresponded to the instructions given to the subjects in the nocebo conditions when histamine was applied for the first time, as much as possible.

2.2.3.2. Pain placebo conditions. The instructions for the subjects in the *pain placebo* and *pain placebo control conditions* were the same as for the itch placebo conditions, except that the word "itch" was replaced by the word "pain," and vice versa.

2.3. Individual psychological characteristics

The individual psychological characteristics of suggestibility, neuroticism, and social desirability were additionally assessed, because these characteristics may affect the magnitude of nocebo and placebo effects [14,21,22]. Therefore, the following validated questionnaires investigating individual psychological characteristics had been filled out within 1 week before the testing took place.

2.3.1. Suggestibility

The Creative Imagination Scale measures the ability to experience suggestions imaginatively [57]. It consists of 10 items, each giving a short description of an event to imagine. For each item, subjects rated the degree of imagining when compared with experiencing the event for real. Items were rated on a 5-point Likert scale, ranging from "totally not the same (0)" to "almost exactly the same (4)." The total score was obtained by calculating the sum of the 10 items. Cronbach alpha of the Creative Imagination Scale in the present study was 0.85.

2.3.2. Imaginative involvement

The Tellegen Absorption Scale was used to measure the subjects' tendency to become deeply involved (absorbed) in everyday activities (34 dichotomous items; true/false). This measure was designed to test the individuals' ability to set reality aside temporarily while engaging in fantasy [49]. Total scores on the scale are the sum of the items identified as "true" on the scale. Cronbach alpha for the Tellegen Absorption Scale in the present study was 0.80.

2.3.3. Social desirability

Social desirability, the tendency to report information colored by social desirability concerns, was measured with the social desirability subscale of the Eysenck Personality Questionnaire [17]. The total score was obtained by calculating the sum of the 22 items, which were rated on a dichotomous scale (yes/no). In the present study, Cronbach alpha was 0.76.

2.3.4. Neuroticism

Neuroticism, which includes the tendency to have more negative outcome expectations, was measured with the neuroticism subscale of the Eysenck Personality Questionnaire [17]. The total score was obtained by calculating the sum of the 22 items, which were rated on a dichotomous scale (yes/no). Cronbach alpha was 0.84 in the present study.

2.4. Statistical analyses

All analyses were performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL, USA). Variables were checked for normal distribution. Variables that were slightly skewed in one of the experimental conditions were transformed by square root transformation, which resulted in a normal distribution. In order to test the main hypotheses of part 1 of this study, general linear model (GLM) MANOVAs were conducted separately for itch and pain scores. In order to test nocebo effects, we conducted MANOVAs, with all dependent variables, for itch and pain scores separately. By using MANOVA tests, the number of tests could be reduced to four because the levels of itch/pain evoked by the four different stimuli could be tested at once. If MANOVA results showed significant between-group effects, additional post hoc ANOVAs were conducted for each stimulus separately to reveal possible differential effects for the effect of the manipulated expectations between the different somatosensory stimuli. For the itch nocebo analysis, mean itch levels evoked by the different sensory stimuli were taken as dependent variables and condition (*itch nocebo condition* [*high expectation*] and *itch nocebo control condition* [*low expectation*]) was taken as an independent variable. The same procedure was applied for the pain nocebo analysis. Moreover, in order to compare the itch nocebo with the pain nocebo condition, GLM multivariate analyses were conducted with the *itch nocebo condition* (*high expectation*) and the *pain nocebo condition* (*high expectation*) as independent variables, and both the itch scores and pain scores separately as dependent variables. In order to investigate possible interaction effects between the different stimuli evoking itch and pain and the suggestions subjects received to manipulate expectations, profile analyses were conducted additionally by applying repeated measures ANOVA with the itch or pain scores for the different stimuli as within-subjects factors and the different groups as between-subject factors.

Additionally, Pearson correlation coefficients were calculated between the levels of expected (after suggestions were given and before stimuli were applied) and experienced (evoked by the stimuli) itch or pain in the *itch or pain nocebo condition* (*high expectation*), respectively.

In order to test the hypotheses of part 2 of this study with repeated applications of histamine, GLM repeated measures ANOVA was conducted. For the itch placebo analysis, itch scores during the first and second application of histamine were taken as within-subject factor, and the itch placebo conditions (*itch placebo* and *itch placebo control*) were taken as between-subject factor. The same analysis was applied for the pain placebo analysis. Moreover, in order to compare itch placebo with pain placebo, GLM repeated measures ANOVA was conducted with the *itch placebo* and the *pain placebo condition* as between-subjects factor, with the itch and pain scores evoked by the first and second application of histamine

separately as within-subjects factor. Placebo analyses were conducted for each experimental condition separately and the interaction effects between the two applications of histamine and experimental condition were calculated. Finally, Pearson correlation coefficients were calculated between the questionnaires measuring individual psychological characteristics of neuroticism, social desirability, imaginative involvement, and suggestibility, and the itch and pain scores in the *itch nocebo condition* (*high expectation*) and the *pain nocebo condition* (*high expectation*), as well as the change score for itch and pain, that is, the difference between the first and second application of histamine, in the *itch* and *pain placebo conditions*.

3. Results

3.1. Part 1: nocebo effects on itch and pain

Regarding part 1, in which we investigated nocebo effects on itch and pain regarding different somatosensory stimuli, we expected that levels of itch evoked by the stimuli would be higher in the *itch nocebo condition* (*high expectation*) than in the *itch nocebo control condition* (*low expectation*) as well as in the *pain nocebo condition* (*high expectation*), and vice versa for pain. Mean current intensities of the electrical tolerance thresholds, a measure tailored to the subjects, did not significantly differ between the nocebo conditions [$F(3,101) = 1.09$, $P = 0.36$].

3.1.1. Nocebo effects on itch

Means and SD of itch evoked by the different sensory stimuli are displayed in Table 1 (see also Fig. 2). MANOVA results of itch nocebo showed that itch levels were significantly higher in the *itch nocebo condition* (*high expectation*) than in the *itch nocebo control condition* (*low expectation*) [Wilks Lambda (Λ) = 0.65, $F(4,51) = 6.85$, $P < 0.001$]. For each stimulus separately, univariate tests (Fig. 2) showed significant effects for higher itch scores in the *itch nocebo* (*high expectation*) than in the *itch nocebo control condition* (*low expectation*), that is, for mechanical stimulation [$F(1,54) = 15.45$, $P < 0.001$], electrical tolerance threshold [$F(1,54) = 9.98$, $P < 0.01$], short electrical stimuli [$F(1,54) = 13.12$, $P = 0.001$], and histamine iontophoresis [$F(1,54) = 12.38$, $P = 0.001$]. In addition to the levels of itch, levels of pain were also significantly higher in the *itch nocebo condition* (*high expectation*) compared to the *itch nocebo control condition* (*low expectation*) [$\Lambda = 0.83$, $F(4,51) = 2.67$, $P < 0.05$], with significant univariate effects in the same direction for electrical tolerance threshold [$F(1,54) = 8.62$, $P < 0.01$] and short electrical stimuli [$F(1,54) = 8.70$, $P < 0.01$], borderline significant effects for histamine iontophoresis [$F(1,54) = 2.91$, $P = 0.09$], and no significant effect for mechanical stimulation [$F(1,54) = 1.08$, $P = 0.30$].

Comparison of itch scores for the *itch nocebo condition* (*high expectation*) and *pain nocebo condition* (*high expectation*) (Table 1) showed that itch scores were significantly higher in the *itch nocebo condition* than in the *pain nocebo condition* [MANOVA $\Lambda = 0.43$, $F(4,64) = 20.88$, $P < 0.001$]. More specifically, univariate analysis showed significantly higher itch scores for the *itch nocebo condition* (*high expectation*) and *pain nocebo condition* (*high expectation*) for all stimuli separately, that is, for mechanical stimulation [$F(1,67) = 22.43$, $P < 0.001$], electrical tolerance threshold [$F(1,67) = 42.01$, $P < 0.001$], short electrical stimuli [$F(1,67) = 52.60$, $P < 0.001$], and histamine iontophoresis [$F(1,67) = 32.34$, $P < 0.001$].

Profile analyses for the different somatosensory stimuli showed no significant interaction effects for evoked pain between the stimuli and the *itch nocebo condition* (*high expectation*) and *itch nocebo control condition* (*low expectation*) [$F(1,55) = 0.98$, $P = 0.33$]. When *itch nocebo* and *pain nocebo conditions* were compared, results showed an interaction effect between itch evoked by the different stimuli and the experimental conditions [$F(1,77) = 7.47$, $P < 0.01$], indicating that the effects on itch evoked may differ across stimuli when comparing itch and pain nocebo suggestions. Inspection of the profile plot indicated that effects were less pronounced for the mechanical stimulation when compared to the other stimuli.

3.1.2. Nocebo effects on pain

Means and SD of pain evoked by the different sensory stimuli are displayed in Table 1. MANOVA results of pain nocebo showed that pain levels were significantly higher in the *pain nocebo condition* (*high expectation*) than in the *pain nocebo control condition* (*low expectation*) [$\Lambda = 0.81$, $F(4,44) = 2.66$, $P < 0.05$]. For each stimulus separately, univariate tests showed significant effects in the same direction, for mechanical stimulation [$F(1,47) = 5.59$, $P < 0.05$], short electrical stimuli [$F(1,47) = 5.75$, $P < 0.05$], and histamine iontophoresis [$F(1,47) = 6.10$, $P < 0.05$]. For the electrical tolerance threshold, the univariate test was borderline significant [$F(1,47) = 3.46$, $P = 0.07$]. In addition to the levels of pain, the levels of itch did not significantly differ between the *pain nocebo* (*high expectation*) and *pain nocebo control condition* (*low expectation*) [$\Lambda = 0.86$, $F(4,44) = 1.73$, $P = 0.16$].

Comparison of pain scores for the *pain nocebo* (*high expectation*) and *itch nocebo condition* (*high expectation*) (Table 1), showed that there was no significant difference between the pain nocebo and itch nocebo conditions [MANOVA $\Lambda = 0.91$, $F(4,64) = 1.51$, $P = 0.21$].

Profile analyses for the different somatosensory stimuli did not show any significant interaction effects for evoked pain between

Table 1
Nocebo effects on itch and pain induced by verbal suggestions (part 1).

Somatosensory stimuli	Itch VAS scores (M ± SD)				Pain VAS scores (M ± SD)			
	Itch nocebo condition	Itch nocebo control condition	Pain nocebo condition	Pain nocebo control condition	Pain nocebo condition	Pain nocebo control condition	Itch nocebo condition	Itch nocebo control condition
Mechanical stimulation								
Monofilaments	0.98 ± 1.18	0.08 ± 0.24	0.12 ± 0.57	0.10 ± 0.27	0.61 ± 0.87	0.20 ± 0.39	0.41 ± 0.77	0.19 ± 0.40
Electrical stimulation								
Electrical tolerance threshold	3.21 ± 2.42	1.37 ± 2.02	0.49 ± 1.24	1.37 ± 2.15	3.09 ± 2.39	1.89 ± 1.34	3.08 ± 2.77	1.17 ± 1.17
Short electrical stimuli	3.51 ± 2.41	1.48 ± 2.34	0.49 ± 0.96	0.89 ± 1.59	3.05 ± 2.13	1.67 ± 1.28	2.79 ± 2.77	0.90 ± 0.98
Chemical stimulation								
Histamine iontophoresis	3.99 ± 1.99	2.13 ± 1.97	1.55 ± 1.47	1.95 ± 1.81	1.18 ± 0.98	0.52 ± 0.61	0.77 ± 1.01	0.40 ± 0.74

Means (M) and standard deviations (SD) of visual analogue scale (VAS) scores for itch and pain in the *itch nocebo condition* (*high expectation*; $n = 36$), the *itch nocebo control condition* (*low expectation*; $n = 20$), the *pain nocebo condition* (*high expectation*; $n = 33$) and the *pain nocebo control condition* (*low expectation*; $n = 16$) evoked by different somatosensory stimuli (mechanical stimulation, electrical stimulation at tolerance threshold, short electrical stimuli, and histamine iontophoresis).

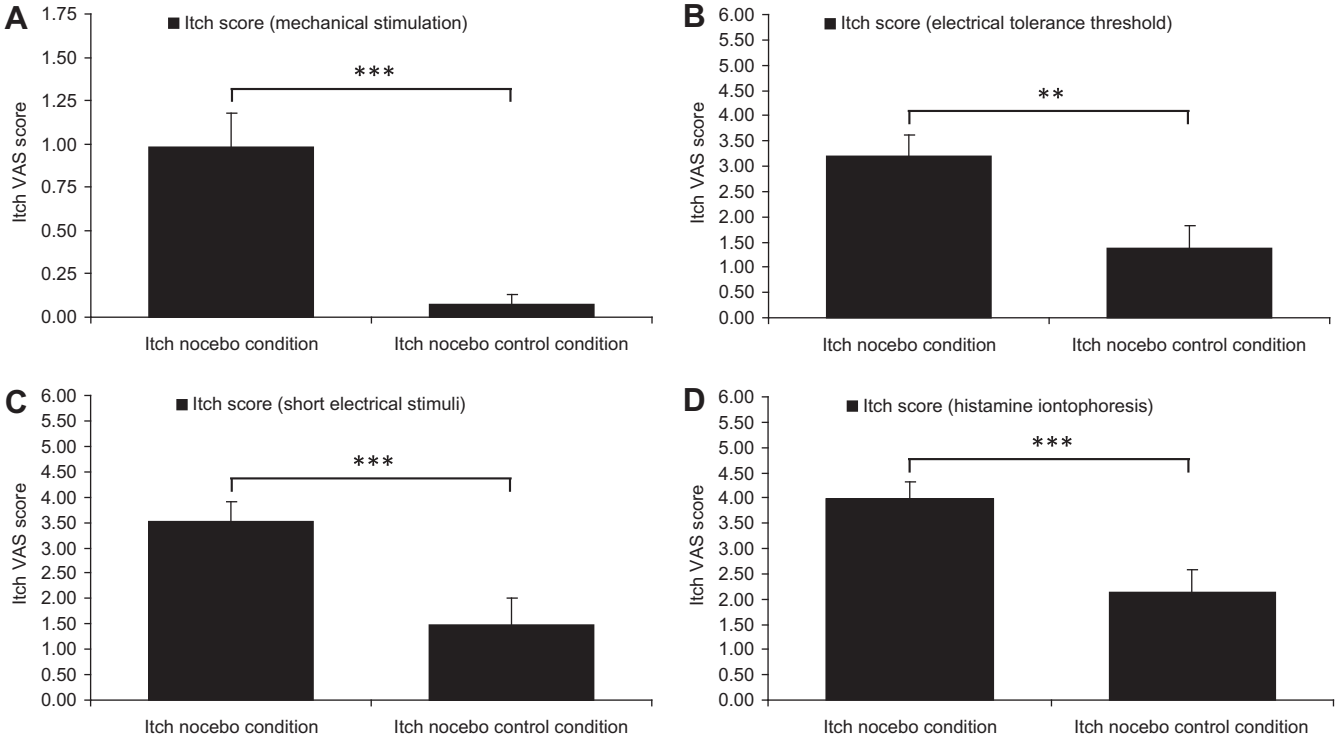

Fig. 2. Mean visual analogue scale (VAS) scores for itch with standard error of the mean (SEM) of subjects in the *itch nocebo condition* (*high expectation*; $n = 36$) and the *itch nocebo control condition* (*low expectation*; nn = 20) for the different somatosensory stimuli applied: mechanical stimulation (A), electrical stimulation at tolerance threshold (B), short electrical stimuli (C), and histamine iontophoresis (D). $^{***}P \leqslant 0.001$. $^{**}P < 0.01$.

the stimuli and the *pain nocebo condition* (*high expectation*) and *pain nocebo control condition* (*low expectation*) [$F(1,55) = 2.50$, $P = 0.12$] or the *pain nocebo condition* (*high expectation*) and *itch nocebo condition* (*high expectation*) [$F(1,77) = 0.02$, $P = 0.89$].

3.1.3. Relationship between expectation and nocebo response

Means and SD of expected levels of itch and pain are displayed in Table 2. Significant correlation coefficients were found between the expected and experienced levels of itch at the electrical tolerance threshold ($r = 0.59$, $P < 0.001$) and with short electrical stimuli ($r = 0.44$, $P < 0.01$) in the *itch nocebo condition* (*high expectation*), meaning that higher expectations of itch for these stimuli were associated with higher levels of experienced itch. Expected levels of pain were only marginally significantly correlated with levels of pain experienced (ie, higher expectations of pain tended to correlate with higher experienced pain) with mechanical stimulation ($r = 0.25$, $P < 0.10$) and at the electrical tolerance threshold ($r = 0.29$, $P = 0.10$) in the *pain nocebo condition* (*high expectation*), but not with the other stimuli.

3.2. Part 2: placebo effects on itch and pain

Regarding part 2, in which we investigated placebo effects regarding two applications of histamine, we expected that subjects in the *itch* and *pain placebo conditions* would show a greater decrease in itch and pain, respectively, than subjects in the respective control conditions, as well as subjects in the other symptom condition, when comparing the first with the second application of histamine.

3.2.1. Placebo effects on itch

Table 3 displays the means and SD of itch evoked by the two applications of histamine in the *itch placebo* and *itch placebo control condition* (see also Fig. 3). Levels of itch were reduced significantly in the two groups [$F(1,34) = 18.42$, $P < 0.001$], but there was no significant interaction effect between the change in itch score and the two conditions [$F(1,34) = 0.01$, $P = 0.91$]. Comparison of the *itch placebo* and the *pain placebo conditions* showed a significant effect of time in the two groups [$F(1,33) = 7.88$, $P < 0.01$], and a significant interaction between the change in itch and the condition [$F(1,33) = 5.84$, $P < 0.05$], indicating that the decrease in itch was larger in the *itch placebo condition* than in the *pain placebo condition*.

3.2.2. Placebo effects on pain

Table 3 displays the means and SD of pain evoked by the two applications of histamine in the pain placebo and pain placebo control conditions. Results showed a significant time effect in the *pain placebo condition* and *pain placebo control condition* [$F(1,31) = 9.94$, $P < 0.01$], while there was no significant between-groups difference in the decrease in pain between the conditions [interaction effect, $F(1,31) = 0.04$, $P = 0.85$]. Comparison of the *pain placebo* and the

Table 2
Pretest expectations of itch and pain to be evoked by the different somatosensory stimuli in the nocebo conditions.

	Itch nocebo condition	Itch nocebo control condition	Pain nocebo condition	Pain nocebo control condition
Pretest expectation of itch (M ± SD)	5.5 ± 1.9	2.7 ± 1.7	1.6 ± 1.6	1.4 ± 1.2
Pretest expectation of pain (M ± SD)	1.8 ± 1.5	1.3 ± 1.3	4.9 ± 1.5	2.1 ± 1.3

Means (M) and standard deviations (SD) of visual analogue scale scores for itch and pain levels expected to be evoked by the different somatosensory stimuli in the different experimental nocebo conditions after the corresponding instructions were given but before application of the stimuli.

Table 3
Placebo effects on itch and pain induced by verbal suggestions (part 2).

		Itch placebo condition	Itch placebo control condition	Pain placebo condition	Pain placebo control condition
1st application of histamine	Itch VAS scores	3.84 ± 2.08	4.18 ± 1.92	0.85 ± 0.85	1.45 ± 1.02
2nd application of histamine	(M ± SD)	2.68 ± 1.63	3.19 ± 2.15	0.58 ± 0.64	1.19 ± 1.06
1st application of histamine	Pain VAS scores	0.78 ± 1.03	0.75 ± 1.02	0.85 ± 0.85	1.45 ± 1.02
2nd application of histamine	(M ± SD)	0.69 ± 0.94	0.86 ± 1.31	0.58 ± 0.64	1.19 ± 1.06

VAS, visual analogue scale.
Means (M) and standard deviations (SD) of itch and pain evoked by histamine applied the first time with the instructions for itch or pain induction (see part 1), and itch and pain evoked by the second application of histamine for which instructions of itch or pain reduction (*itch placebo condition*, $n = 20$; *pain placebo condition*, $n = 15$) or neutral itch or neutral pain instructions (*itch placebo control condition*, $n = 16$; *pain placebo control condition*, $n = 18$) were given.

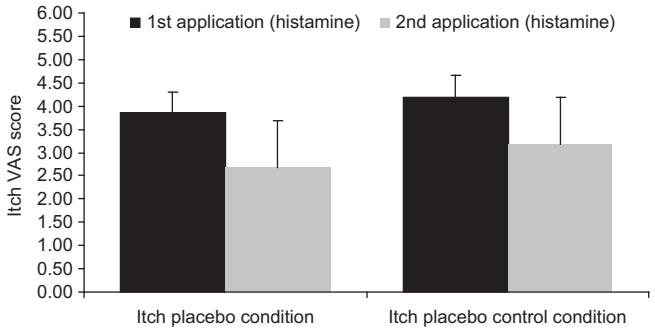

Fig. 3. Mean visual analogue scale (VAS) scores for itch with standard error of the mean (SEM) of subjects in the *itch placebo condition* ($n = 20$) and the *itch placebo control condition* ($n = 16$) for the first (part 1) and second (part 2) application of histamine.

itch placebo conditions revealed an almost significant time effect [$F(1,33) = 2.80$, $P = 0.10$], but there was no interaction effect between the change in pain score between the conditions [$F(1,33) = 0.54$, $P = 0.47$].

3.3. Individual psychological characteristics

All Pearson correlation coefficients between the personality characteristics neuroticism, social desirability, imaginative involvement, and suggestibility, and itch and pain evoked by the four stimuli in the nocebo conditions for itch and pain in part 1 of this study were not significant. There were also no significant correlations between the change score for itch and pain in *the itch placebo* and *pain placebo conditions* and personality characteristics (neuroticism, social desirability, imaginative involvement, and suggestibility) in part 2 of this study.

4. Discussion

The present study showed, for the first time, that nocebo effects can be induced on itch, besides pain, by manipulating expectations through verbal suggestions regarding different somatosensory stimuli. Verbal suggestions designed to induce a placebo effect on itch resulted in a significantly greater decrease in itch than when pain placebo suggestions were given.

In part 1, we investigated nocebo effects on itch and pain by manipulating subjects' expectations of itch and pain by giving verbal suggestions about itch or pain that would be evoked by different somatosensory stimuli. We found that subjects who received verbal suggestions to induce high pain expectations reported significantly more pain than subjects who received verbal suggestions inducing low pain expectations. These results are consistent with earlier findings on verbal suggestions inducing nocebo effects on pain [2,7,11,47]. More importantly, we showed that nocebo effects could be induced on itch by verbal suggestions regarding different ambiguous somatosensory stimuli [50,51]. Subjects who received verbal suggestions inducing high itch expectations experienced significantly higher levels of itch evoked by the somatosensory stimuli than subjects who received verbal suggestions inducing low itch expectations. Our results are consistent with previous studies, which showed that subjects experienced more itch when instructions exaggerating itch were given compared to neutral instructions, or when they listened to a lecture about itch compared to a neutral lecture [36,44].

The nocebo effects induced by verbal suggestions appeared to be stronger for itch than for pain. This might indicate that itch may be more susceptible to suggestion than pain, for example, itch is known to be induced by watching other people scratching or by talking about itch [36]. Another explanation might be the opposite reflex pattern seen in itch and pain [42]. For example, subjects tend to withdraw from a painful stimulus or activity, whereas itch is predominantly a trigger for heightened physical activity, such as scratching [55]. In addition, itch and pain are influenced by different affective and motivational components, and despite the many similarities in sensitization mechanisms, the processing of itch and pain occurs via separate neurological pathways [28,43,48]. Itch distinguishes from pain by a specific neuronal pathway such as a histamine-dependent itch (mechano-insensitive) and an unspecific itch pathway that probably differentiates on the pattern of brain activation [28,43]. Furthermore, expectations about pain can alter central pain modulation [7,20,24,52], which processes may be different for itch expectations. Also, the type or intensity of the somatosensory stimuli used may play a role, for example, the stimuli may evoke somewhat higher levels of itch than pain (eg, histamine). Several studies have shown that expectations of pain influence pain perception [9,19,32,41,56], and strong correlations between expected and experienced pain have been reported [35]. Response expectancies may lead to a cognitive readjustment of the appropriate behavior and also play a key role in nocebo and placebo effects [31,38]. Endogenous opioid systems and the cholecystokininergic pronociceptive system are supposed to play a role in the analgesia by expectations, since naloxone can antagonize these effects and cholecystokinin antagonists are capable of potentiating analgesia [5,6]. In the present study, expectations of itch and pain were significantly or marginally significantly correlated with experienced itch and pain evoked by some of the stimuli, which partly supports that conscious expectation may be a possible mediator in some nocebo- and placebo-related effects [9,38].

In part 2 we investigated the role of verbal suggestions in placebo effects on itch and pain regarding two applications of histamine. Itch levels decreased to a greater extent when suggestions of itch reduction were given than when suggestions of pain reduction were given, while the decrease in itch was not significantly different when it was suggested that itch would be reduced in comparison to neutral suggestions. The repeated application of histamine might have induced a habituation effect, resulting in a decreased response to the stimulus [34]. The lack of a pain placebo response is probably a consequence of the type of stimulus used,

as the mean pain scores for the first application of histamine were below 1.5. Furthermore, although earlier research has shown that verbal suggestions can be effective in inducing placebo effects on pain [1,9,19,38], effects were much stronger in combination with a conditioning procedure [10,33]. Finally, placebo effects have been shown to be stronger when contextual factors, for example, by imitating a clinical setting, are included [15].

Besides verbal suggestions, negative (nocebo) or positive (placebo) expectations for itch or pain can also be induced by conditioning. As an additional effect of conditioning to verbal suggestions was found regarding the magnitude of the placebo effect [10,33], literature indicates that conditioning does not have such an additional effect in nocebo effects on pain [11,37,47]. Future research should investigate whether conditioning could lead to nocebo and placebo responses for itch. For example for placebo, multiple itch stimuli of decreasing intensity could be applied in combination with the suggestion that an itch-reducing substance was added.

Individual psychological characteristics of positive or negative expectation tendencies (eg, neuroticism or catastrophizing), suggestibility (eg, imagination), and social desirability may influence nocebo or placebo responses [14,21,22]. However, in the present study we did not find any significant correlation with the psychological characteristics. Future research could further clarify the specific role of expectation-related personality characteristics in nocebo and placebo effects on itch and pain, for example, optimism and pessimism [21,22].

The present study had some limitations that should be taken into consideration. First, nocebo and placebo effects require, by definition, the administration of inert (placebo) substances. Since an inert substance was administered only in the placebo experiment, the effects of the nocebo condition rather reflect *nocebo-related effects* of verbal suggestions after a stimulus induction [4]. In future studies, inert substances, for example, nocebo cream, should also be included to investigate the effects of the nocebo substance in addition to nocebo suggestions only. Moreover, various stimuli were applied to investigate nocebo effects (part 1), while we used histamine only to investigate placebo effects (part 2). Consequently, it is not yet possible to generalize the findings of part 2 among other stimuli, and the results of the nocebo and placebo experiment cannot be compared directly. Second, since we manipulated expectations for itch and pain simultaneously, some interaction effects between itch and pain, such as pain inhibitory effects on itch [28,48], cannot be excluded. Since stimuli were applied in the same order for all subjects, we further cannot exclude cross-over (habituation or sensitization) effects due to the preceding stimuli. However, we minimized the interaction effects between stimuli by applying the stimuli with sufficient intervals in between, based on applications of these stimuli in previous studies [50–52]. Third, not all our stimuli may be applicable to induce itch and pain to the same extent, in view of, for example, the low levels of pain induced by histamine in the placebo conditions. In addition, an interaction effect was found with regard to the strength of the itch nocebo effects across the different somatosensory stimuli. Inspection of the profile plot suggests that verbal suggestion in the *itch* versus *pain nocebo condition* is less effective for itch evoked for the lowest-intensity stimulation (mechanical stimulation). Future research should look into the efficacy of verbal suggestion in inducing placebo and nocebo effects regarding different stimuli modalities. Fourth, in addition to the control conditions with low expectations for itch and pain in part 1, an additional control condition with neutral suggestions without any expectations might be included in future research. Fifth, brain imagining studies showed that placebo responses for pain were accompanied by changes in several brain regions [39,40] and future research could, next to itch and pain levels, include additional measures of placebo and nocebo responding, such as activation patterns of brain areas involved [7,8]. Sixth, since patients with chronic pain and itch have been shown to react differently to sensory stimuli, as, for example, chronic pain patients have been shown to sensitize differently to repeated pain stimuli than healthy subjects [13,46,51], expectations might elicit distinct patterns of nocebo or placebo responses in patients compared to healthy subjects. Research of nocebo and placebo effects in patients with chronic itch or pain can provide insight into the role of expectations in clinical worsening or improvement to develop therapies to alter expectations in order to decrease their suffering from chronic itch or pain.

In conclusion, we showed that, besides pain, itch nocebo effects can be induced by only giving verbal suggestions. The perception of different ambiguous stimuli can be influenced by negative suggestions, in such a way that negative expectations can adversely influence the intensity of itch or pain experienced. Our results emphasize the importance of expectations in nocebo effects on itch, and further suggest that negative suggestions may possibly be more effective in inducing itch nocebo responses than pain nocebo responses. In line with earlier findings of verbal suggestions on pain, we did find only indirect evidence for a placebo effect on itch in comparison to pain. Future research should focus on the role of expectations induced by conditioning and verbal suggestions in nocebo and placebo effects on itch, in particular in patients with chronic itch. In the long term, these findings may facilitate the development of therapeutic strategies to reduce itch by manipulating patients' expectations.

Conflict of interest

There are no financial or other arrangements that might lead to a conflict of interest.

References

[1] Amanzio M, Pollo A, Maggi G, Benedetti F. Response variability to analgesics: a role for non-specific activation of endogenous opioids. Pain 2001;90:205–15.
[2] Arntz A, Claassens L. The meaning of pain influences its experienced intensity. Pain 2004;109:20–5.
[3] Atanassoff PG, Brull SJ, Zhang J, Greenquist K, Silverman DG, LaMotte RH. Enhancement of experimental pruritus and mechanically evoked dysesthesiae with local anesthesia. Somatosens Mot Res 1999;16:291–8.
[4] Benedetti F. Mechanisms of placebo and placebo-related effects across diseases and treatments. Annu Rev Pharmacol Toxicol 2008;48:33–60.
[5] Benedetti F. The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. Pain 1996;64:535–43.
[6] Benedetti F, Amanzio M, Maggi G. Potentiation of placebo analgesia by proglumide. Lancet 1995;346:1231.
[7] Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: unraveling the mechanisms of the nocebo effect. Neuroscience 2007;147:260–71.
[8] Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK. Neurobiological mechanisms of the placebo effect. J Neurosci 2005;25:10390–402.
[9] 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;23:4315–23.
[10] Colloca L, Benedetti F. How prior experience shapes placebo analgesia. Pain 2006;124:126–33.
[11] Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. Pain 2008;136:211–8.
[12] Colloca L, Tinazzi M, Recchia S, Le Pera D, Fiaschi A, Benedetti F, Valeriani M. Learning potentiates neurophysiological and behavioral placebo analgesic responses. Pain 2008;139:306–14.
[13] Curatolo M, Arendt-Nielsen L, Petersen-Felix S. Central hypersensitivity in chronic pain: mechanisms and clinical implications. Phys Med Rehabil Clin N Am 2006;17:287–302.
[14] De Pascalis V, Chiaradia C, Carotenuto E. The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental setting. Pain 2002;96:393–402.
[15] Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of context effects on health outcomes: a systematic review. Lancet 2001;357:757–62.
[16] Enck P, Benedetti F, Schedlowski M. New insights into the placebo and nocebo responses. Neuron 2008;59:195–206.

[17] Eysenck HJ, Eysenck SBG. Manual of the Eysenck Personality Scales (EPS Adult). London: Hodder & Stoughton; 1991.
[18] Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. Lancet 2010;375:686–95.
[19] Flaten MA, Aslaksen PM, Finset A, Simonsen T, Johansen O. Cognitive and emotional factors in placebo analgesia. J Psychosom Res 2006;61:81–9.
[20] Flaten MA, Simonsen T, Olsen H. Drug-related information generates placebo and nocebo responses that modify the drug response. Psychosom Med 1999;61:250–5.
[21] Geers AL, Helfer SG, Kosbab K, Weiland PE, Landry SJ. Reconsidering the role of personality in placebo effects: dispositional optimism, situational expectations, and the placebo response. J Psychosom Res 2005;58:121–7.
[22] Geers AL, Kosbab K, Helfer SG, Weiland PE, Wellman JA. Further evidence for individual differences in placebo responding: an interactionist perspective. J Psychosom Res 2007;62:563–70.
[23] Goetz CG, Leurgans S, Raman R, Stebbins GT. Objective changes in motor function during placebo treatment in PD. Neurology 2000;54:710–4.
[24] Goffaux P, de Souza JB, Potvin S, Marchand S. Pain relief through expectation supersedes descending inhibitory deficits in fibromyalgia patients. Pain 2009;145:18–23.
[25] Green AD, Young KK, Lehto SG, Smith SB, Mogil JS. Influence of genotype, dose and sex on pruritogen-induced scratching behavior in the mouse. Pain 2006;124:50–8.
[26] Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: clinical and research application in neuropathic pain states. Pain 2007;129:256–9.
[27] Ikoma A, Handwerker H, Miyachi Y, Schmelz M. Electrically evoked itch in humans. Pain 2005;113:148–54.
[28] Ikoma A, Steinhoff M, Stander S, Yosipovitch G, Schmelz M. The neurobiology of itch. Nat Rev Neurosci 2006;7:535–47.
[29] Kidd BL, Urban LA. Mechanisms of inflammatory pain. Br J Anaesth 2001;87:3–11.
[30] Kirsch I. Are drug and placebo effects in depression additive? Biol Psychiatry 2000;47:733–5.
[31] Kirsch I. Response expectancy theory and application: a decennial review. Appl Prev Psychol 1997;6:69–79.
[32] Kirsch I. How expectancies shape experience. Washington, DC: American Psychological Association; 1999.
[33] 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;128:31–9.
[34] McSweeney FK, Murphy ES. Sensitization and habituation regulate reinforcer effectiveness. Neurobiol Learn Mem 2009;92:189–98.
[35] Montgomery GH, Kirsch I. Classical conditioning and the placebo effect. Pain 1997;72:107–13.
[36] Niemeier V, Kupfer J, Gieler U. Observations during an itch-inducing lecture. Dermatol Psychosom 1999;1:15–8.
[37] Petrovic P. Placebo analgesia and nocebo hyperalgesia—two sides of the same coin? Pain 2008;136:5–6.
[38] Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G, Benedetti F. Response expectancies in placebo analgesia and their clinical relevance. Pain 2001;93:77–84.
[39] Price DD, Craggs J, Verne GN, Perlstein WM, Robinson ME. Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. Pain 2007;127:63–72.
[40] 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.
[41] Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, Nicholls SS. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental design. Pain 1999;83:147–56.
[42] Schmelz M. Complex interactions between pain and itch. Pain 2006;124:9–10.
[43] Schmelz M. Itch and pain. Neurosci Biobehav Rev 2010;34:171–6.
[44] Scholz OB, Hermanns N. Illness behavior and cognitions influence the perception of itching of patients suffering from atopic dermatitis. Z Klin Psychol 1994;23:127–35.
[45] Simone DA, Alreja M, LaMotte RH. Psychophysical studies of the itch sensation and itchy skin (“alloknesis”) produced by intracutaneous injection of histamine. Somatosens Mot Res 1991;8:271–9.
[46] Smith BW, Tooley EM, Montague EQ, Robinson AE, Cosper CJ, Mullins PG. Habituation and sensitization to heat and cold pain in women with fibromyalgia and healthy controls. Pain 2008;140:420–8.
[47] Staats P, Hekmat H, Staats A. Suggestion/placebo effects on pain: negative as well as positive. J Pain Symptom Manage 1998;15:235–43.
[48] Stander S, Schmelz M. Chronic itch and pain—similarities and differences. Eur J Pain 2006;10:473–8.
[49] Tellegen A, Atkinson G. Openness to absorbing and self-altering experiences (absorption), a trait related to hypnotic-susceptibility. J Abnorm Psychol 1974;83:268–77.
[50] Van Laarhoven AI, Kraaimaat FW, Wilder-Smith OH, Evers AWM. Role of attentional focus on bodily sensations in sensitivity to itch and pain. Acta Derm Venereol 2010;90:46–51.
[51] Van Laarhoven AIM, Kraaimaat FW, Wilder-Smith OH, van de Kerkhof PC, Cats H, van Riel PL, Evers AW. Generalized and symptom-specific sensitization of chronic itch and pain. J Eur Acad Dermatol Venereol 2007;21:1187–92.
[52] Van Laarhoven AIM, Kraaimaat FW, Wilder-Smith OH, van de Kerkhof PCM, Evers AWM. Heterotopic pruritic conditioning and itch—analogous to DNIC in pain? Pain 2010;149:332–7.
[53] Vase L, Robinson ME, Verne GN, Price DD. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients. An empirical investigation. Pain 2003;105:17–25.
[54] Verhoeven EW, Kraaimaat FW, van de Kerkhof PC, van Weel C, Duller P, van der Valk PG, van den Hoogen HJ, Bor JH, Schers HJ, Evers AW. Prevalence of physical symptoms of itch, pain and fatigue in patients with skin diseases in general practice. Br J Dermatol 2007;156:1346–9.
[55] Verhoeven L, Kraaimaat F, Duller P, van de Kerkhof P, Evers A. Cognitive, behavioral, and physiological reactivity to chronic itching: analogies to chronic pain. Int J Behav Med 2006;13:237–43.
[56] Wager TD. Expectations and anxiety as mediators of placebo effects in pain. Pain 2005;115:225–6.
[57] Wilson SC, Barber TX. The creative imagination scale as a measure of hypnotic responsiveness: applications to experimental and clinical hypnosis. Am J Clin Hypn 1978;20:235–49.