Expectations and positive emotional feelings accompany reductions in ongoing and evoked neuropathic pain following placebo interventions

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Abstract

Research on placebo analgesia and nocebo hyperalgesia has primarily included healthy subjects or acute pain patients, and it is unknown whether these effects can be obtained in ongoing pain in patients with chronic pain caused by an identifiable nerve injury. Eighteen patients with postthoracotomy neuropathic pain were exposed to placebo and nocebo manipulations, in which they received open and hidden administrations of pain-relieving (lidocaine) or pain-inducing (capsaicin) treatment controlled for the natural history of pain. Immediately after the open administration, patients rated their expected pain levels on a mechanical visual analogue scale (M-VAS). They also reported their emotional feelings via a quantitative/qualitative experiential method. Subsequently, patients rated their ongoing pain levels on the M-VAS and underwent quantitative sensory testing of evoked pain (brush, pinprick, area of hyperalgesia, wind-up-like pain). There was a significant placebo effect on both ongoing (P = .009 to .019) and evoked neuropathic pain (P = .0005 to .053). Expected pain levels accounted for significant amounts of the variance in ongoing (53.4%) and evoked pain (up to 34.5%) after the open lidocaine administration. Furthermore, patients reported high levels of positive and low levels of negative emotional feelings in the placebo condition compared with the nocebo condition ($P \leqslant .001$). Pain increases during nocebo were nonsignificant (P = .394 to 1.000). To our knowledge, this is the first study to demonstrate placebo effects in ongoing neuropathic pain. It provides further evidence for placebo-induced reduction in hyperalgesia and suggests that patients' expectations coexist with emotional feelings about treatments.

Keywords

Emotional feelings; Expectation; Neuropathic pain; Nocebo hyperalgesia; Placebo analgesia

1. Introduction

Few systematic mechanistic studies of placebo analgesia in chronic pain patients exist, and they have primarily been conducted in patients with pain from irritable bowel syndrome [12], [30], [53], [64], [65] and [66], where the underlying pathophysiology remains unclear [34] and [46]. Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system [28] and is characterized by ongoing pain and evoked pain [7]. Evoked pains, ie, allodynia and hyperalgesia, often extend into areas outside those innervated by the lesioned nerve (secondary areas) as a consequence of central sensitization. Only one

study in postthoracotomy patients has investigated mechanisms of placebo analgesia in neuropathic pain [44]. In this study, however, placebo reduced only the area of secondary hyperalgesia. As the intensity of ongoing pain was low, it is presently unclear whether placebo effects reduce ongoing neuropathic pain. Furthermore, no studies have investigated nocebo effects in neuropathic pain.

Across studies of placebo analgesia, the contribution of psychological factors has been examined [4]. Expectations of low pain levels have generally been shown to contribute to placebo-induced analgesia in healthy subjects and pain patients [1], [5], [6], [42], [56] and [64]. Emotional factors such as a reduction in negative affect, including fear, anxiety, and depression, have been associated with placebo analgesia [19], [20], [38], [39] and [43], whereas especially high levels of anxiety have been associated with increased nocebo hyperalgesia [17]. These factors are typically examined by use of standardized questionnaires in which patients rate their position on predefined emotions that may only indirectly relate to their immediate experience [23]. Therefore, in order to further our understanding of how emotional feelings and expectations influence patients' ongoing pain, it would be helpful to use an experiential method. Here, patients are directly asked about their personal experience in the moment when they knowingly receive a treatment [50] and [63]. The open–hidden approach, in which active medication is given either openly (ie, in full view of the patient) or hidden (ie, without the patient's knowledge) [1], [5] and [9], is especially relevant for this purpose as it enables the investigation of placebo effects in an experimental setting that mimics the doctor's administration of treatments to a patient in clinical practice.

Hence, we aimed at extending our previous findings by exposing patients with moderate levels of neuropathic pain to not only placebo but also nocebo interventions to investigate how these interventions influenced ongoing and evoked pain. Specifically, we administered active treatments to the painful area by use of the open–hidden approach [44] along with verbal suggestions for pain relief and pain increase. The difference in effect between the open and the hidden administrations of the pain-relieving treatment controlled for the natural history of pain represents the placebo effect, and the similar administrations of the pain-inducing treatment represents the nocebo effect. Furthermore, in relation to the placebo and nocebo interventions (ie, open treatment administration along with verbal suggestions), patients rated their expected pain levels on the mechanical visual analogue scale (M-VAS). Their emotional feelings were also sampled by a new quantitative/qualitative experiential method [48] and [50] to further characterize qualitative aspects of emotional feelings during placebo and nocebo interventions.

2. Materials and methods

2.1. Subjects

Eighteen patients aged 18 years or older with peripheral neuropathic pain after anterior thoracotomy or video-assisted thoracoscopic surgery 1 to 10 years before their participation were included in the study. The patients were recruited from the Department of Cardiothoracic and Vascular Surgery and the Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark. Patients were screened for inclusion if they reported persistent ongoing neuropathic pain corresponding to an average score of pain intensity of $\geqslant$3 on a numeric rating scale (NRS, 0–10). Neuropathic pain is defined, according to the International Association for the Study of Pain, as "pain caused by a lesion or disease of the somatosensory system" [28], and we included patients with definite or probable neuropathic pain using the neuropathic pain grading system [55]. Pain should be located in an area of sensory abnormality compatible with a nerve injury after thoracic surgery. In addition, a clinical examination was performed, including a skin inspection and evaluation of pain during movement and the presence of muscle trigger points to exclude any obvious

nociceptive pain. The exclusion criteria were neurological or psychiatric disorders, known allergies to local anesthetics, skin disease in the upper part of the body, or treatment with class 1 antiarrhythmic drugs. Patients receiving medication on an irregular basis were asked to withdraw from the medication 12 h before testing, and patients receiving regular medication were asked not to change the dose of medication during the study period. All patients provided signed informed consent and received no payment for their participation except reimbursement for their travel expenses. In the consent form, the patients were told that they could be informed about the study and the results of the study once the study was terminated. The study was approved by the local ethics committee for the Central Denmark Region (m-20110269) and the Danish Data Protection Agency.

2.2. General conceptualizations

In the current study, the open–hidden design was used to investigate placebo and nocebo effects [1], [5], [6] and [36]. In this design, active pharmacological agents are administered either in full view of the patient (open) or without the patient's knowledge (hidden), and typically controlled for a natural history of pain (no treatment) in order to test if changes in pain levels are due to placebo and nocebo manipulations rather than spontaneous fluctuations in pain [18]. In the current study, the analgesic agent lidocaine was used to investigate the placebo effect, whereas the hyperalgesic agent capsaicin was used to investigate the nocebo effect. The open administration of lidocaine was combined with a verbal suggestion for pain relief (placebo): "The agent you have just been given is known to powerfully reduce pain in some patients," whereas the open administration of capsaicin was combined with a verbal suggestion to increase pain (nocebo): "The agent you have just been given is known to powerfully increase pain in some patients." Thus, the placebo effect was calculated as the difference in pain levels between the open and the hidden administration of lidocaine controlled for the no-treatment pain levels. Likewise, the nocebo effect was calculated as the difference in pain levels between the open and the hidden administration of capsaicin controlled for the no-treatment pain levels.

2.3. Conditions and verbal suggestions

Each patient went through 3 test days with different conditions: nocebo (open and hidden administrations of capsaicin), placebo (open and hidden administrations of lidocaine), and control (no administration of treatment). Thus, each treatment day consisted of a baseline–open condition of either lidocaine or capsaicin and a baseline–hidden condition of either lidocaine or capsaicin. The control condition was analogous to the treatment conditions and consisted of a baseline–control 1 condition and a baseline–control 2 condition, which allowed for a test of how the pain developed over time. The difference in pain between the baseline–open lidocaine condition and the baseline–hidden lidocaine condition controlled for the natural history of pain was conceptualized as the placebo effect. Likewise, the difference in pain between the baseline–open capsaicin condition and the baseline–hidden capsaicin condition controlled for the natural history of pain was conceptualized as the nocebo effect (Fig. 1).

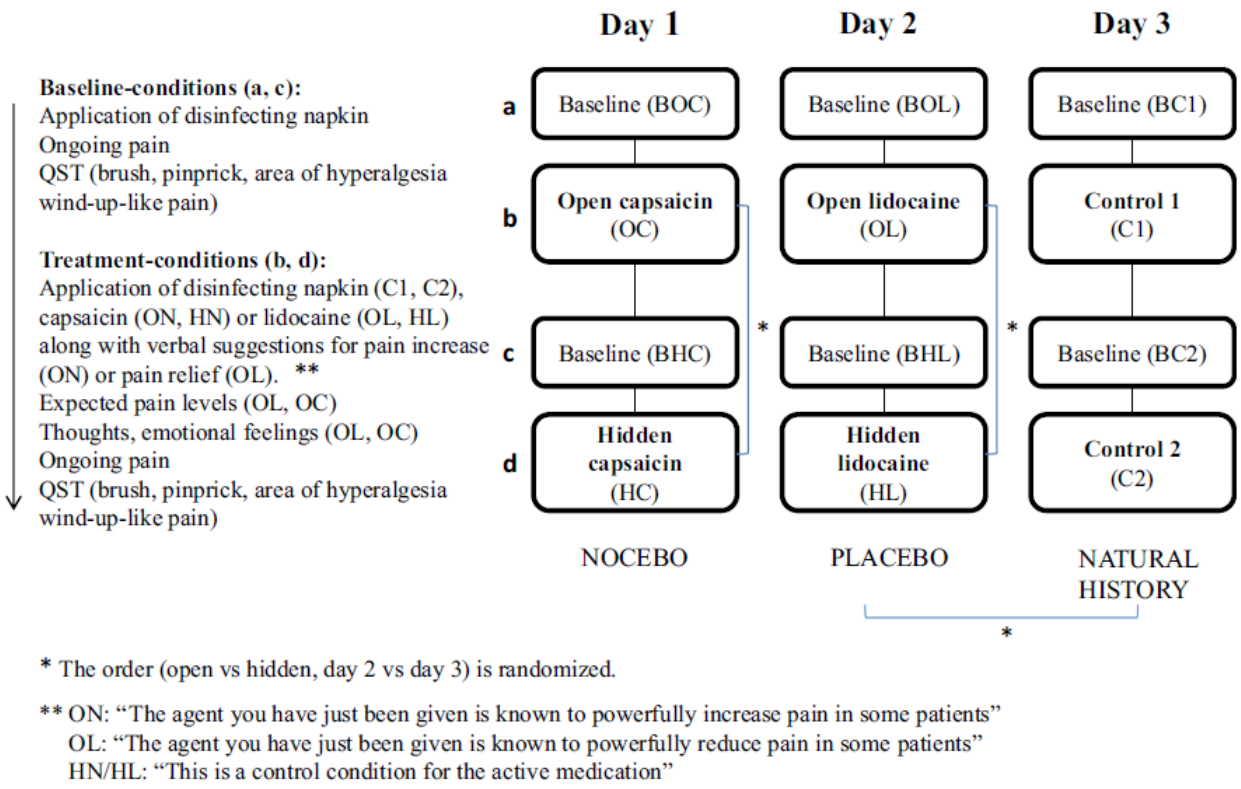

Fig. 1. *Study design. Each patient participates in all 3 test days and each day includes 2 baseline conditions and 2 treatment conditions (open and hidden administrations of treatment) or 2 control conditions.*

The investigator told the patients that the study was an investigation of how their pain levels would fluctuate when they received different painful and nonpainful stimuli as well as pain-relieving and pain-inducing treatments. In the baseline–control conditions, patients were told: "We will test your response to different types of stimuli in order to get a better understanding of how (your) pain is processed." Before the baseline–open condition of lidocaine, patients were told: "An active medication that has been shown to be effective for some types of pain will be tested." Lidocaine, which was used in the placebo intervention, was given in full view of the patients, who were told: "The agent you have just been given is known to powerfully reduce pain in some patients." In the baseline–open condition of capsaicin, patients were told: "An active medication that has been shown to increase some types of pain will be tested." Capsaicin, which was used in the nocebo intervention, was given in full view of the patients, who were told: "The agent you have just been given is known to powerfully increase pain in some patients." In the baseline–hidden condition of both lidocaine and capsaicin, the patients received the same information as in the baseline–control condition and were also told: "This is a control condition for the active medication." The active medication was administered without the patients' knowledge. Hence, the placebo intervention consisted of the administration of lidocaine along with verbal suggestions for pain relief, whereas the nocebo intervention consisted of administration of capsaicin along with verbal suggestions for pain increase. After the verbal suggestions, patients reported on the psychological measures and went through quantitative sensory testing (QST).

2.4. Medication

Active medication was administered in both the placebo and nocebo interventions. Lidocaine (cutaneous solution, 5%, 2 mL) was administered in the placebo intervention in accordance with previous studies [1] and [44], and capsaicin was administered (cream, 10%, 0.05 mL) in the nocebo intervention. The open and hidden administrations of lidocaine and capsaicin were embedded in the standard treatment procedure. Before the QST, the test area was cleaned with a disinfecting napkin (Mediq Denmark; 82% ethanol, 2% glycerol, 0.5% chlorhexidine), so lidocaine or capsaicin could easily be applied to the napkin with or without the patients' knowledge. In the baseline–control conditions, the disinfecting napkin was used according to the standard treatment procedure (no treatment was applied). In the open conditions, the investigator applied lidocaine or capsaicin to the napkin in full view of the patient and gave verbal suggestions for pain relief or pain increase. In the hidden conditions, lidocaine and capsaicin had already been applied to the napkin without the patient's knowledge, and the investigator pretended to use the napkin for disinfection only. Five patients participated in a pilot test of this procedure and were informed that we were interested in knowing how they experienced a new type of disinfecting napkins that we wanted to include in our standard practice. The pilot test showed that it was not possible to detect the lidocaine or capsaicin on the napkin. Moreover, the solutions of lidocaine and capsaicin did not cause any numbness, skin irritation, warmth, or coolness, which might have unblinded the procedure. Thus, the hidden administrations were not known to the patients.

Lidocaine was chosen as the active pain-relieving treatment because it has been shown that topical application of 5% lidocaine gel relieves pain in some neuropathic pain conditions [58]. This is in accordance with a previous open–hidden study that used metamizol with some, but not a definitive, effect on pain after thoracotomy [1] and with our previous study [44].

Topical capsaicin was chosen as the active pain-inducing treatment because it exerts its effect at the site of application and has no systemic adverse effects [13]. The initial burning sensation felt on the application of the capsaicin limits the amount of cream that can be applied at one time without unblinding the patient in the hidden condition. The high concentration (10%) in a small dosage was chosen to increase the likelihood that the patients would experience an increase in pain without any visual or sensory indication (eg, redness of the skin) that a cream had been applied, which could reveal the hidden administration. The dosage was slightly lower than the one used in other studies, in which the dosage had to induce a stable level of pain and hyperalgesia [40]. The patients were not preselected to be capsaicin responders [41]. The administration of pharmacological agents was blinded for the patients, but due to the close coupling of treatment administration and verbal suggestions for pain relief, it was not blinded for the experimenter.

2.5. Quantitative sensory testing

A test area in close proximity to the surgical site was identified. The area had to be approximately 5 × 10 cm in size and placed in the painful area but outside scar tissue. A similar control area was identified on the contralateral side. Both areas were marked with a pencil, and photos were taken to document the test sites. Test stimuli were applied to the affected and nonaffected side of thorax in randomized order. Outcome measurements were obtained in the following order: ongoing pain, brush-evoked pain, pinprick-evoked pain, area of pinprick hyperalgesia, and windup-like pain to pinprick stimulation. The order of the test stimuli was not randomized but started with the gentlest stimulation in order to test for tactile allodynia that was not confounded by evoked sensitization [22] and [33]. The QST was performed by GLP.

2.6. Pain measures

Ongoing and evoked pain intensity and unpleasantness were measured with the M-VAS. Patients were instructed how to rate their pain intensity and unpleasantness according to standardized written statements [52]. It was explained to them that the experience of pain consists of a sensory (intensity) and affective (unpleasantness) dimension, which may be experienced differently [55]. Verbal anchors served to establish the distinction between the dimensions. The M-VAS sensory scale was anchored at the left by the descriptors “no pain sensation” and at the right by “the most intense pain sensation imaginable.” Likewise, the M-VAS unpleasantness scale was anchored by the descriptors “not at all unpleasant” and “the most unpleasant sensation imaginable.”

2.6.1. Ongoing pain

Ongoing pain intensity and unpleasantness were the primary outcome measures. The pain ratings were obtained after the treatment was administered and before the QST was performed in order to measure the effect of the open and hidden administrations of treatments controlled for the natural history of pain on pain levels (Fig. 1).

2.6.2. Evoked pain

The evoked pain measures were selected based on the findings in the first study of placebo effects in neuropathic pain [44], and a special emphasis was given to wind-up-like pain and areas of secondary hyperalgesia because the combination of these QST measures and ongoing pain can serve as indices of central sensitization [35].

Brush-evoked pain intensity and unpleasantness were rated by gently stroking a brush (brush 0.5, Senselab; Somedic, Stockholm, Sweden) over the test area twice (2 s in all). Pinprick-evoked pain intensity and unpleasantness were rated by bending a handheld Semmes-Weinstein monofilament (Stoelting, IL; No. 5.88; nominal bending force 744.9 mN) once in the center of the most painful part of the test area. The area of pinprick hyperalgesia on the affected side of the thorax was assessed with the same handheld Semmes-Weinstein monofilament. The patient was asked to look away from the test site while the investigator stimulated from the periphery toward the center of the painful area in steps of 1 cm at a rate of 1 cm s−1. The patient reported when the sensation changed to tenderness or pain and a mark was made with a pencil. In this way, the area of pinprick hyperalgesia was mapped. The area was photographed, transferred to plastic wrap and then to paper, and calculated in square centimeters using a standard program (Quantify; KLONK, Ringsted, Denmark).

Temporal summation to mechanical stimulation was determined with a handheld Semmes-Weinstein monofilament (No. 5.88; nominal bending force 744.9 mN). Repetitive stimulation was performed at 2 Hz for 30 s, including a total of 60 stimuli. During the stimulation, patients were asked to rate their pain intensity on an electrical visual analogue scale (E-VAS) in order to get a measure of how their pain varied (area under the curve). After the stimulation, patients were asked to rate their worst pain intensity and worst pain unpleasantness during the stimulation on the M-VAS.

2.7. Psychological measures

2.7.1. Expected pain levels

Ratings of expectancy were obtained with the same M-VAS scales that were used to assess ongoing and evoked pain. Expected pain intensity and unpleasantness were measured prospectively by asking the patients immediately after the open administration of a treatment and before it had taken effect: “What do

you expect your level of pain intensity/unpleasantness to be during this session?" and specifically in relation to each test: "What do you expect your level of pain intensity/unpleasantness to be in relation to brush stimulation/pinprick stimulation/windup-like pain?" The scale for the expected pain levels has been validated previously and used in former studies of placebo analgesia [44], [49], [56], [64] and [65]. In relation to the area of hyperalgesia, expectancy was measured by asking patients: "Do you expect your area of hyperalgesia to be the same, larger, or smaller than before (ie, compared with baseline)?"

2.7.2. Positive and negative emotional feelings

Quantitative and qualitative measures of the patients' direct experience of the open treatment administrations were obtained by use of an idiographic, experiential method [25], [50] and [51]. Emotions are closely related to thoughts, particularly those related to the likelihood of pain relief and they contain positive and negative emotional feelings [50]. Emotional feelings refer to the subjective component of emotions—that is, how the emotions are experienced by the patients as opposed to their outward expression. Hence, in the placebo and nocebo interventions, the patients were asked to report retrospectively any positive and/or negative emotional feelings from the previous minutes during which the intervention was performed. In short, the patients were asked to rate their emotional feelings on an M-VAS anchored with "no positive/negative emotional feelings" at one end and "the most intense positive/negative emotional feelings" at the other end. In addition, they were asked to qualitatively describe their experiences during the intervention with a few words [24], [25] and [50]. The scales were uniform for all patients, who were encouraged, but not forced, to report the qualitative features of their experience. Further information on the experiential method, data collection, and analyses is provided in Appendix 1.

It is important to note that because expected pain levels were obtained prospectively, they were used as a predictor, whereas the assessment of expectation during the qualitative–quantitative assessment of emotional feelings (obtained retrospectively) was used to determine whether expectations coexist with emotional feelings about treatments. Thus, the study was not designed to make direct comparisons between expected pain levels and emotional feelings.

2.8. Procedure

The study took place at the Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark. The patients were greeted in the waiting room by the investigator, who wore a white uniform, and escorted them to the examination room. Here they were introduced to the study and gave their signed informed consent to participate. The investigator took time to establish a good patient–practitioner relationship [27] and [30], and the patient's medical history and detailed descriptions of the patient's development of pain were obtained.

The test days were separated by at least 3 days in order for any effect of the treatment to wear off. The nocebo and placebo test days started with a baseline condition to control for the daily variability of pain followed by a treatment condition (either open or hidden administration). The second baseline condition served to control for carryover effects.

The nocebo test day was always the first test day as a pilot test had suggested that it was difficult to induce a nocebo effect if the patient had experienced a placebo effect first. The order of the placebo test day and the control test day and the order of the open and hidden administrations were randomized. The randomization was performed by flipping a coin before each patient's participation in the investigation. A

coin was flipped once to decide whether the second test day was the placebo condition or the control condition, and twice to decide the order of the open and hidden administrations of lidocaine and capsaicin.

Each test day proceeded as follows. First, the investigator and the patient conversed for approximately 20 min about the patient's pain and general well-being; then the pain rating scales were introduced, and the program of the day was outlined in order to familiarize the patient with the study. Second, the patient was invited to sit in a hospital bed in a supine position for the testing. The patient was asked to rate his or her ongoing pain intensity and unpleasantness, and the test site was marked, photographed, and cleaned with a disinfecting napkin. In the baseline (Fig. 1a, c) and control conditions (Fig. 1b, d; day 3), the disinfecting napkin was applied alone, but in the treatment conditions (Fig 1b, d), lidocaine or capsaicin was applied with the patient's knowledge in the open condition and without the patient's knowledge in the hidden condition. Immediately after the application of the open treatment and before it had taken effect, the patient was asked to rate his or her expected pain levels and emotional feelings. Then the patient rested for 10 min in order for the medication to take effect in the treatment conditions. Thereafter, ratings of ongoing pain intensity and unpleasantness were obtained again, and the QST began. This procedure was repeated after a pause of 45 min to allow for both an open and a hidden condition of either lidocaine or capsaicin on one test day (BC1-C1/BC2-C2; BOL-OL/BHL-HL; BOC-OC/BHC-HC; Fig. 1). Pilot testing had assured that the effect of the medication had worn off, and the second baseline condition also served to control for any carryover effect of the first treatment condition.

2.9. Statistical analyses

The placebo effect and the nocebo effect were calculated as the difference between the open and the hidden administrations of lidocaine and capsaicin, respectively, compared with the natural history of pain. Specifically, both effects were calculated as difference scores between ratings in the baseline–control condition (average of the 2 conditions: [baseline 1 minus control 1 + baseline 2 minus control 2)/2]; ΔControl), baseline–open condition (baseline minus open; ΔBOL-OL for placebo and ΔBOC-OC for nocebo), and baseline–hidden condition (baseline minus hidden; ΔBHL-HL for placebo and ΔBHC-HC for nocebo). The baseline–control condition was calculated as the average of the 2 control conditions (baseline–control 1 and baseline–control 2) as the baseline–control condition was repeated in order to parallel the baseline–treatment conditions where both open and hidden treatment administrations were performed on the same test day. The difference scores were used as the primary outcome measures in the statistical analyses. The 3 conditions (control, open, hidden) for placebo and nocebo, respectively, were compared using repeated-measures analyses of variance (ANOVA). Separate analyses for pain intensity and unpleasantness ratings of ongoing pain, brush-evoked pain, pinprick-evoked pain, the area of hyperalgesia, and wind-up-like pain were conducted. In all analyses, control (ΔControl), open (ΔBOL-OL or ΔBOC-OC), and hidden (ΔBHL-HL or ΔBHC-HC) served as within-subject variables for each condition. Omnibus F tests were followed by post hoc tests with Bonferroni correction for multiple comparisons. Sphericity was also assessed and when the assumption was not verified, the Greenhouse-Geisser correction was applied.

Effect sizes were calculated for each of the pain outcome measures in the following manner. Difference scores between baseline–open lidocaine and baseline–hidden lidocaine (ΔBOLOL-BHLHL), between baseline–open capsaicin and baseline–hidden capsaicin (ΔBOCOC-BHCHC), and between baseline–control 1 and baseline–control 2 (ΔControl1–2) were computed. The means and standard deviations from these values were used for the calculation of effect sizes according to Cohen's d (d = (Xcontrol − Xplacebo)/pooled standard deviation) for placebo and (d = (Xcontrol − Xnocebo)/pooled standard

deviation) [8]. Accordingly, for the calculation of the effect sizes in relation to placebo, ΔBOLOL-BHLHL and ΔControl1–2 were used and in relation to nocebo ΔBOCOC-BHCHC and ΔControl1–2 were used. A value of 0.2 is considered a small effect, a value of 0.5 a medium effect, and a value of 0.8 a large effect [8].

Expected pain levels in the 3 conditions were compared using repeated-measures ANOVA. To assess the a priori hypotheses about the effects of expected pain levels on pain intensity and unpleasantness after the open administrations of lidocaine and capsaicin, linear regression analyses were conducted. Expected pain levels in the open conditions (ie, OL and OC) were used as independent variables. Separate regressions were conducted for all measures of pain intensity and unpleasantness in relation to the independent variables. A similar strategy has been applied in previous placebo analgesia research [44], [56] and [64]. The measures of the patients' direct experience and emotional feelings were analyzed quantitatively by calculating means and standard deviations of the M-VAS ratings and qualitatively by sampling the reported experiences and emotional feelings. Categories were not determined a priori as the experiential method explores experience as it is lived [25] and [26]. Patients did not receive extensive training in differentiating between thoughts and emotional feelings, and during the analyses, it became clear that the patients' emotional feelings were typically about expectations of pain relief and/or of receiving a treatment, and therefore elements of thoughts were incorporated in this category. For example, in the context of receiving a treatment, the patients' emotions usually occurred together with thoughts (ie, "I hope this is going to work"). In the analyses, the categories positive and negative emotional feelings were used (Appendix 1). The intensity of each of the 2 categories (positive emotional feeling, negative emotional feeling) was compared in the placebo vs the nocebo intervention via paired t test. SPSS software, version 19 (IBM, Armonk, NY), was used, and the level of significance was set at $P < .05$. The results are expressed in mean values ±SD.

3. Results

3.1. Patient characteristics

Ten men and 8 women with an average age of 56.8 years (range 32–65 years) participated in the study. Seven patients were operated on the left side of the thorax and 11 patients on the right side. When the patients entered into the study and at the beginning of all test days, their levels of ongoing pain intensity and unpleasantness fulfilled the inclusion criteria of $\geqslant 3$ (NRS, 0–10) (average pain intensity, 3.42 (1.54); average pain unpleasantness, 3.34 (1.24)). Eight patients were on regular medication and still reported levels of ongoing pain above the inclusion criteria.

3.2. Placebo effects in ongoing and evoked pain

3.2.1. Ongoing pain

The results of the repeated-measures ANOVA for ongoing pain intensity and unpleasantness in relation to the placebo effect are presented in Table 1. The post hoc tests using the Bonferroni correction revealed a significant reduction in pain intensity ($P = .009$) and unpleasantness ($P = .019$) in the open (ΔBOL-OL) vs the hidden (ΔBHL-HL) administration of lidocaine when controlled for no treatment (ΔControl). The ongoing pain intensity across the 3 conditions for both baseline and treatment is illustrated in Fig. 2. There was no significant difference in the control (ΔControl) vs the hidden condition (ΔBHL-HL) ($P = 1.000$ for pain intensity and unpleasantness), indicating no significant effect of lidocaine on ongoing pain compared with no treatment. The Cohen's d value for ongoing pain intensity and unpleasantness was 1.01 and 0.86, respectively. No gender effects were observed in relation to ongoing pain (all P values between .873 and

.921). Thus, a large and highly significant placebo effect was obtained in ongoing neuropathic pain intensity and unpleasantness.

Table 1. *Pain outcome measures in relation to placebo and nocebo conditions.*

Table 1
Pain outcome measures in relation to placebo and nocebo conditions.

Repeated measures ANOVA	*df*	Error	*F*	P^1	Comparison (P^2)
Placebo					ΔBOL-OL vs ΔBHL-HL
Ongoing pain intensity	2	34	11.284	<.0005*	.009*
Ongoing pain unpleasantness	2	34	9.379	.001*	.019*
Brush intensity (G)	1.919	32.626	2.641	.088	1.000
Brush unpleasantness (G)	1.656	28.152	2.490	.109	.799
Pinprick intensity	2	34	15.736	<.0005*	.004*
Pinprick unpleasantness	2	34	15.111	<.0005*	.004*
Area of hyperalgesia (G)	1.967	33.442	43.993	<.0005*	<.0005*
Wind-up-like pain, area under curve	2	34	5.566	.008*	.053*
Wind-up-like pain, worst pain intensity (G)	1.702	28.930	20.729	<.0005*	<.0005*
Wind-up-like pain, worst pain unpleasantness (G)	1.927	32.763	16.436	<.0005*	.001*
Nocebo					ΔBOC-OC vs ΔBHC-HC
Ongoing pain intensity	2	34	3.263	.051	.394
Ongoing pain unpleasantness	2	34	1.017	.372	1.000
Brush intensity	2	34	0.891	.420	.767
Brush unpleasantness	2	34	0.367	.695	1.000
Pinprick intensity (G)	1.791	30.451	0.090	.895	1.000
Pinprick unpleasantness (G)	1.724	29.309	0.394	.647	1.000
Area of hyperalgesia (G)	1.669	26.701	4.102	.034	.552
Wind-up-like pain, area under curve	2	30	0.122	.886	1.000
Wind-up-like pain, worst pain intensity (G)	1.641	27.904	0.002	.995	1.000
Wind-up-like pain, worst pain unpleasantness (G)	1.668	28.357	0.006	.988	1.000

G = Greenhouse-Geisser correction; P^1 = general *P* value for ANOVA model; P^2 = *P* value for comparison between open and hidden administration of treatments when controlled for no treatment. All *P* values are reported with Bonferroni corrections.
* Statistically significant ($P < 0.05$).

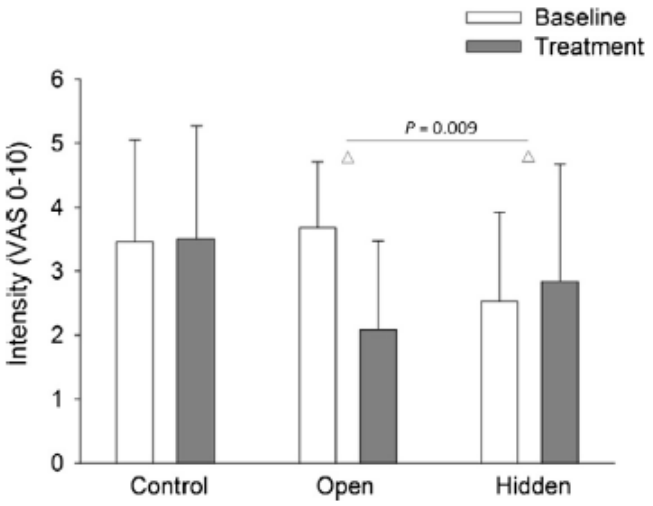

Fig. 2. *Placebo effect on ongoing neuropathic pain. Ratings of pain intensity across control, open and hidden administrations of lidocaine are illustrated. A significant main effect (P < .0005) was observed, as well as a significant specific effect between open and hidden administration, controlled for the natural history of pain.*

3.2.2. Evoked pain

The results of the repeated-measures ANOVA for evoked pain intensity and unpleasantness in relation to the placebo effect are presented in Table 1. With regard to pinprick-evoked pain, the post hoc tests using the Bonferroni correction showed a significant reduction in both pain intensity and unpleasantness (P =

.004) in the open (ΔBOL-OL) vs the hidden (ΔBHL-HL) condition when controlled for no treatment (ΔControl). In relation to the area of hyperalgesia, the post hoc tests using Bonferroni correction revealed a significantly smaller area of hyperalgesia (P < .0005) in the open (ΔBOL-OL) vs the hidden (ΔBHL-HL) condition when controlled for no treatment (ΔControl). The area of hyperalgesia across the 3 conditions for both baseline and treatment is illustrated in Fig. 3. Also, the post hoc tests using Bonferroni correction revealed a significant reduction in worst pain intensity (P < .0005) and unpleasantness (P = .001) in the open (ΔBOL-OL) vs the hidden (ΔBHL-HL) condition when controlled for no treatment (ΔControl). Worst pain intensity during wind-up-like pain stimulation across the 3 conditions for both baseline and treatment is illustrated in Fig. 4. Only a strong trend toward significance (P = .053) was found in the open (ΔBOL-OL) vs the hidden (ΔBHL-HL) condition for the area under the curve during wind-up-like pain stimulation when controlled for the natural history of pain (ΔControl). In sum, large and significant placebo effects were obtained in pinprick-evoked pain, the area of hyperalgesia, and wind-up-like pain. The Cohen's d values for brush-evoked pain intensity and unpleasantness was 0.27. and 0.44, respectively, and for pinprick-evoked pain intensity and unpleasantness it was 1.15 and 1.2. With regard to wind-up-like pain, a d value of 0.89 was obtained for the area under the curve and for worst pain intensity and unpleasantness, the d values were 1.63 and 1.71. In relation to the area of hyperalgesia, the d value was 2.01.

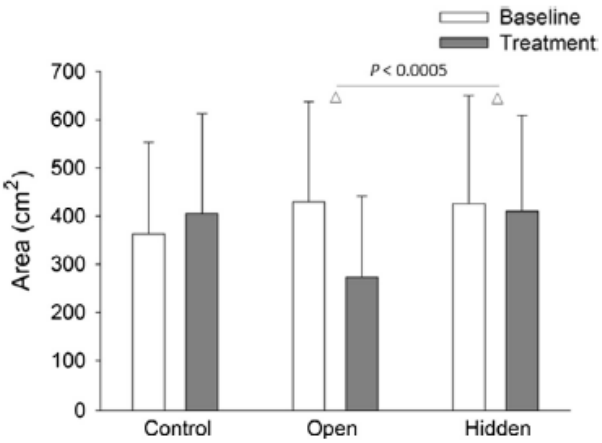

Fig. 3. *Placebo effect on the area of hyperalgesia. Ratings of area of hyperalgesia across control, open, and hidden administrations of lidocaine are illustrated. A significant main effect (P < .0005) was observed, as well as a significant specific effect between the open and the hidden administration, controlled for the natural history of pain.*

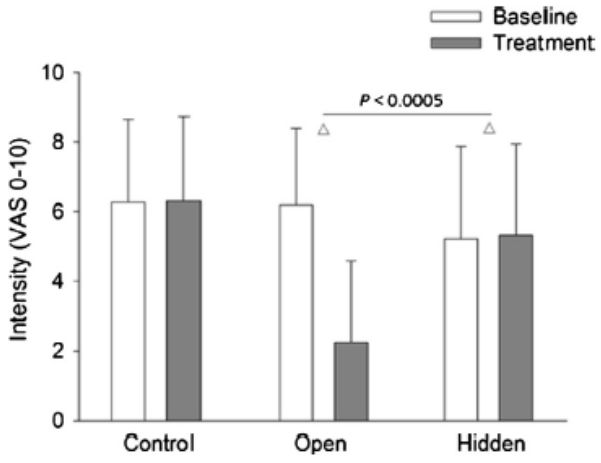

Fig. 4. *Placebo effect on worst pain during wind-up-like pain stimulation. Ratings of pain intensity across control, open, and hidden administrations of lidocaine are illustrated. A significant main effect (P < .0005) was observed, as well as a significant specific effect between the open and the hidden administration, controlled for the natural history of pain.*

Across the evoked pain measures, there was no significant difference in the control (ΔControl) vs the hidden condition (ΔBHL-HL) (P = .100 to .999 for pain intensity and unpleasantness), indicating no significant effect of lidocaine compared with no treatment on pinprick-evoked pain, the area of hyperalgesia, and wind-up-like pain. Also, no gender effects were observed across these evoked pain measures (all P values between .433 and .825).

3.3. Nocebo effects in relation to ongoing and evoked pain

The results of the repeated-measures ANOVA for ongoing and evoked pain intensity and unpleasantness in relation to the nocebo effect are presented in Table 1. No significant differences in either ongoing pain or any of the evoked pain measures between the 3 conditions (ΔControl, ΔBOC-OC, ΔBHC-HC) were found. Thus, no nocebo effects were obtained in ongoing pain, brush-evoked pain, pinprick-evoked pain, the area of hyperalgesia, or wind-up-like pain. The ongoing pain intensity across the 3 conditions for both baseline and treatment is illustrated in Fig. 5.

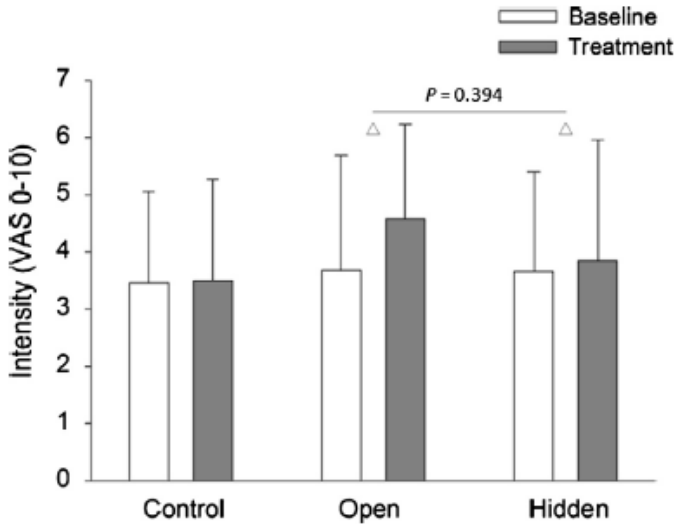

Fig. 5. *Nocebo effect on ongoing neuropathic pain. Ratings of pain intensity across control, open, and hidden administrations of capsaicin are illustrated. A borderline significant main effect (P = .051) was observed, while there was a nonsignificant specific effect between the open and the hidden administration, controlled for the natural history of pain.*

Effect sizes were also calculated for the nocebo effects in relation to ongoing and evoked pain. For ongoing pain, a d value of −0.43 and −0.40 was obtained for intensity and unpleasantness. For evoked pain, d values of −0.30 and −0.12 for intensity and unpleasantness after brush, d values of −0.36 and 0.18 for intensity and unpleasantness after pinprick, and d values of 0.17, 0.16 and 0.30 for wind-up-like pain area under the curve, worst pain intensity and unpleasantness, respectively. For the area of hyperalgesia, a d value of −0.42 was found.

3.4. Psychological factors related to pain during the placebo intervention

3.4.1. Expectation ratings

There was a significant difference between expected pain levels in the open, hidden, and control conditions (P < .001). Patients generally expected and experienced lower pain levels during the open administration of lidocaine compared to the hidden administration and the control group (Table 2). The results of the

regression analyses relating expected pain levels to pain intensity and unpleasantness during the placebo intervention are presented in Table 3. In regard to ongoing pain, expected pain levels significantly predicted 53.4% of the variance in pain intensity and 32% of the variance in pain unpleasantness after the open administration of lidocaine. In relation to evoked pain, expected pain levels significantly predicted 26.8% to 34.5% of pinprick-evoked pain after open lidocaine administration. For wind-up-like pain measures, expectancy significantly predicted 24.4% of the variance in the area under the curve but did not significantly predict worst pain intensity or unpleasantness. Furthermore, 77.1% of the patients (14 of 18 patients) expected a reduction in the area of hyperalgesia after the open lidocaine administration.

Table 2. *Expected and experienced pain levels during open and hidden administration of lidocaine and capsaicin.*

Pain	Open lidocaine	Hidden lidocaine	Open capsaicin	Hidden capsaicin	Control
Expected pain intensity	2.24 (1.46)	3.35 (1.70)	5.01 (1.97)	4.33 (1.77)	4.74 (2.01)
Expected pain unpleasantness	1.92 (1.34)	3.27 (1.59)	4.62 (2.14)	4.36 (1.94)	4.51 (1.98)
Experienced pain intensity	2.08 (1.38)	2.84 (1.83)	4.58 (1.65)	3.85 (2.11)	3.36 (1.75)
Experienced pain unpleasantness	1.89 (1.45)	2.89 (1.79)	4.48 (2.07)	3.77 (2.18)	3.29 (1.66)

Data are reported as mean (SD).

Table 3. *Expectancy in relation to ongoing and evoked pain during the placebo intervention.*

Model	*B*	R^2	*F*	*P*
Ongoing pain				
Pain intensity	0.694	0.534	18.338	.001
Pain unpleasantness	0.613	0.320	7.537	.014
Evoked pain				
Pinprick intensity	0.609	0.345	8.441	.010
Pinprick unpleasantness	0.549	0.268	5.856	.028
Wind-up-like pain, area under the curve	155.417	0.244	4.854	.044
Wind-up-like pain, worst pain intensity	0.507	0.201	4.033	.062
Wind-up-like pain, worst pain unpleasantness	0.472	0.171	3.305	.088

B = unstandardized coefficient; R^2 = coefficient of determination; $P < .05$.

3.4.2. Experiential ratings and descriptions of emotional feelings

With regard to the data that combined the sampling of the patients' qualitative descriptions and quantitative ratings within these descriptions, the intensity of the positive emotions reported in the open administration of lidocaine was on average 7.0 (2.76) on the M-VAS, whereas the intensity of negative emotional feelings was on average 0.34 (0.65) (Fig. 6). Thus, the patients reported a much higher intensity of positive than negative emotional feelings after the open administration of lidocaine. The descriptions corroborated the ratings by showing that the most commonly expressed emotional feelings in the open condition were excitement, hope, and positive expectations. They were described by 11 of 18 patients in the open condition, whereas no patients reported descriptions of negative emotional feelings. As an illustration, one patient said, "I am hoping that the cream will bring relief," while another patient reported, "This is better than Christmas Eve."

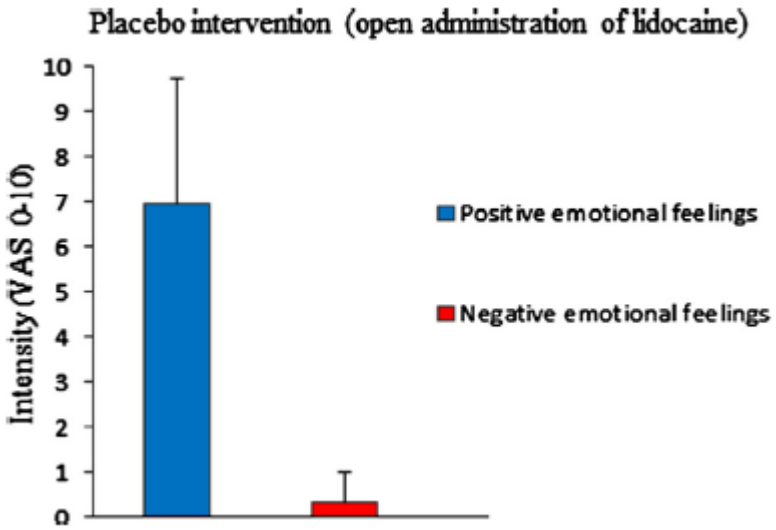

Fig. 6. *Means and standard deviations for positive and negative emotional feelings in the placebo intervention. The emotions encompass elements of thoughts. See Appendix 1 for further information.*

3.5. Psychological factors related to pain during the nocebo intervention

3.5.1. Expectation ratings

In the open administration of capsaicin, the patients rated the average expected pain intensity and expected pain unpleasantness to 5.01 (1.97) and 4.62 (2.14), respectively, whereas their average experienced pain intensity and pain unpleasantness was 4.6 (1.65) and 4.5 (2.07), respectively. Compared with the open administration of lidocaine, these ratings indicate that the patients expected higher pain levels in the nocebo intervention than during the placebo intervention.

Because no nocebo effects were found, it can be debated whether the psychological factors should be analyzed. We compared expected pain levels across the 3 conditions (open, hidden, control) and performed regression analyses of expectations in relation to ongoing and evoked pain in the open administration of capsaicin, and all of these comparisons were not significant (data not shown).

3.5.2. Experiential ratings and descriptions of emotional feelings

We found it interesting to analyze the experiential data as they might hold important information for the understanding of the results in relation to the nocebo intervention. The intensity of the negative emotional feelings reported in the open administration of capsaicin was on average 3.3 (1.7) on the M-VAS compared with 3.2 (2.5) for the intensity of positive emotional feelings (Fig. 7). Hence, the patients reported a similar intensity of positive and negative emotional feelings after the open capsaicin administration. This profile is very different from what was found during the placebo intervention (Fig. 6). The qualitative descriptions indicate that the patients most commonly expressed emotional feelings about pain and related unpleasantness. They were described by 10 of 18 patients, and only 1 patient expressed positive emotional feelings of hope and expectations. This can be illustrated by a patient who said, “I was thinking of burning skin and the duration of the burning pain,” and by another patient who reported “a sensation of unpleasantness, like touching a thistle or a stinging nettle.”

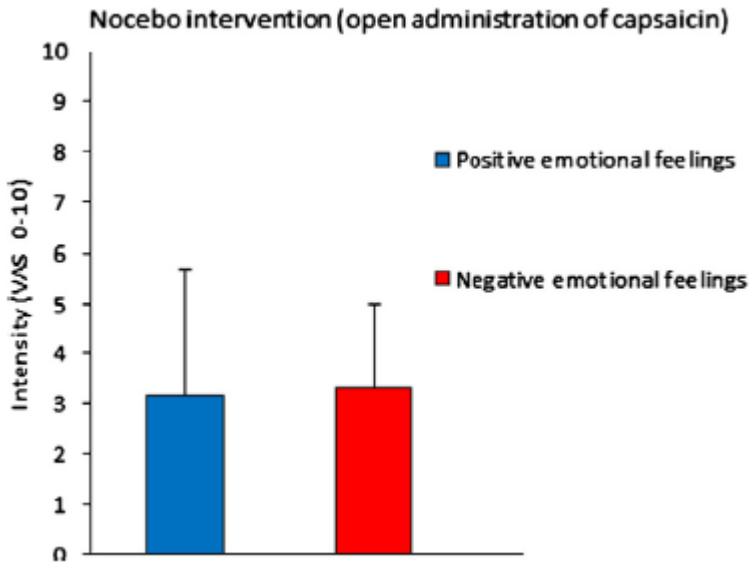

Fig. 7. *Means and standard deviations for positive and negative emotional feelings in the nocebo intervention. The emotions encompass elements of thoughts. See Appendix 1 for further information.*

3.6. Direct comparison of emotional feelings in placebo and nocebo interventions

The paired t test revealed that the intensity of positive emotional feelings was significantly higher in the placebo intervention than in the nocebo intervention ($P = .001$), whereas the intensity of negative emotional feelings was significantly lower in the placebo intervention than in the nocebo intervention ($P < .001$).

4. Discussion

The results clearly indicate large placebo effects, but no nocebo effects, for ongoing and evoked pain such as wind-up-like pain and secondary hyperalgesia in patients with probable or definite neuropathic pain [62] after thoracic surgery (Cohen's $d > 0.8$). Expected pain levels predicted a substantial amount of the variance in pain intensity and unpleasantness in relation to the open administration of lidocaine. Expectations of low pain levels coexisted with the patients' experiences of high levels of positive emotional feelings and low levels of negative emotional feelings during the placebo intervention. In contrast, the same patients experienced higher levels of negative emotional feelings, but still moderately high levels of positive emotional feelings during the nocebo intervention. Expectation is generally seen as essential to placebo analgesia [21], and our experiential results suggest that expectations are accompanied by mainly positive emotional feelings targeted toward the therapeutic intervention. Thus, expectations occur within an emotional context [54].

4.1. Placebo effects in relation to ongoing and evoked pain

To our knowledge, this is the first study to demonstrate a well-controlled placebo effect in ongoing neuropathic pain. The patients experienced a highly significant reduction in both pain intensity and

unpleasantness in the open vs the hidden condition when controlled for no treatment. In our previous study [44], we did not find a placebo effect in ongoing neuropathic pain, and we hypothesized that this was due to the patients experiencing pain levels below 3 on the M-VAS on the test day, but not during recruitment. Our present findings support the notion that when patients experience pain levels in accordance with the recommendations for experimental studies of chronic pain [15], placebo effects can reduce ongoing pain levels.

This is also the first study to show that placebo effects exert inhibitory effects on 3 measures that are likely to be associated with hyperalgesia and central sensitization: (1) maximum wind-up-like pain intensity, (2) area of secondary hyperalgesia, and (3) ongoing clinical pain [2], [35] and [37]. Previous studies have suggested that wind-up-like pain and central sensitization are related to secondary hyperalgesia and help maintain ongoing clinical pain [2], [35], [37], [60] and [61]. The results of the current study extend those of our previous study, in which we found only a reduction in hyperalgesic areas [44], and add to the increasing evidence that at least some forms of placebo analgesia reflect antihyperalgesic mechanisms. Although there may be several possible central neural mechanisms by which this occurs, an efficient one might include inhibition of dorsal horn nociceptive neurons that are sensitized. This mechanism would be consistent with an fMRI neuroimaging study showing that placebo effects are accompanied by a reduction in neural activity in the human spinal dorsal horn [16]. The magnitude of the placebo effect was larger for evoked pain than for ongoing clinical pain as can be seen in for example the effect sizes. This finding is consistent with other studies [66] and [68], and it may at least in part be related to measurement issues such as the precision of measurement of ongoing clinical pain (especially with few ratings) vs precision of some QST measures associated with clinical pain.

We did not find an effect of the active treatment alone, indicating that the observed findings may primarily be influenced by placebo-related factors optimizing the efficacy of the treatment. A possible limitation of the study could be that it was not double-blinded. However, as can be seen in Table 2, patients expected lower pain levels in the open compared with the hidden administration of lidocaine, and likewise, they expected higher pain levels in the hidden compared with the open administration of capsaicin, thereby suggesting that the hidden administrations of agents were in fact hidden to the patients.

4.2. Nocebo effects in relation to ongoing and evoked pain

There was a nonsignificant increase of ongoing pain in the open vs the hidden administration of capsaicin, but we did not observe any significant nocebo effects in evoked pain (Cohen's d values between −0.43 and 0.30). There may be several explanations for these negative findings. The dosage of capsaicin may not have been strong enough to produce a pain increase despite the high concentration. Also, it may be argued that recruitment of only capsaicin responders [41] and the use of the preliminary skin heating would have enhanced the effect of capsaicin and thereby have increased the patients' pain [14] and [45]. This assumption is supported by the finding that capsaicin alone did not result in a significant pain increase. However, it is worth noting that lidocaine in itself did not lead to a pain decrease. Hence, the findings may not be directly related to capsaicin and the specific administration of it. In fact, only 2 studies have so far investigated nocebo effects in chronic pain patients and both found small, but nonsignificant nocebo effects [31] and [64], proposing that placebo and nocebo manipulations might exert differential effects in chronic pain conditions and/or that it may be more difficult to obtain nocebo effects in chronic pain patients tested in a clinical setting than in healthy volunteers tested in a laboratory setting [10], [11], [29] and [32].

4.3. Expectations and emotional feelings during the placebo intervention

Expected pain levels significantly predicted both ongoing and evoked pain during the open administration of lidocaine and they also contributed to pain levels in the hidden and control conditions. The experiential analyses of emotions during the placebo intervention indicated that the patients' expectations of pain relief coexisted with their emotional feelings in so far as patients had high levels of positive emotions and low levels of negative emotions along with expectations of low pain levels. The patients primarily reported excitement, hope, and expectations for the treatment to have an effect, which is in accordance with previous experiential findings [63] suggesting that patients are actively engaged in initiating experienced pain relief in relation to open treatment administration [50].

The finding that patients had high levels of positive and low levels of negative emotional feelings during the open administration of lidocaine is in contrast to our previous studies showing that only low levels of negative affect were significantly related to pain in the placebo condition [44], and it is partly in contrast with a previous study in which the behavioral data showed that positive emotions were nonsignificantly related to placebo, whereas negative emotions were significantly related to placebo effects [59]. In the previous studies, emotional feelings were measured via standardized questionnaires such as the Positive Affect Negative Affect Scale (PANAS), in which patients were asked to rate the extent to which they experienced predefined emotions. Hence, one explanation of the seemingly contradictory results may be that during the open administration of treatments, patients do not experience the positive emotional feelings predefined in the PANAS, but instead positive emotional feelings that are captured by open reports of their immediate experience. The experiential approach may therefore be helpful in further specifications of the emotional content and valence of patients' expectations. Thus, in relation to chronic pain patients it appears to be important to understand that expectations are not neutral, they are emotional and therefore it is relevant to further investigate how expectations and emotional feelings interact in treatment effects.

4.4. Expectations and emotional feelings during the nocebo intervention

During the nocebo intervention, the patients expected higher pain levels than during the placebo intervention, but the expected pain levels were not related to the nonsignificant increase in ongoing pain in the open vs the hidden administration of capsaicin controlled for the natural history of pain. The study was not specifically designed to test for the modulatory effects of negative and positive emotions, but the experiential data may still partially explain the observed findings. In the open administration of capsaicin, patients reported higher levels of negative emotions compared with the open administration of lidocaine, but the intensity of their positive emotional feelings was still high and similar to the placebo intervention. Hence, although patients did experience negative emotional feelings during the nocebo intervention, there was no indication of excessively negative expectations and emotional feelings in relation to pain as seen in pain catastrophizing [57], [67] and [68]. Instead, patients appeared to be primarily focused on the sensations of pain and unpleasantness. It is plausible that aspects of the treatments and pain stimuli (capsaicin) were not aversive enough for the patients to develop markedly negative expectations, emotional feelings, and therefore nocebo effects. We tried to adjust for this by placing the nocebo conditions on the first test day, by recruiting patients with minimal prior experience with pain treatment, and by mirroring the positive and negative verbal suggestions. However, the experiential data suggest that this was not sufficient. Future studies of nocebo effects in chronic pain patients may therefore benefit from procedures and manipulations that are perceived as more aversive and intrusive in relation to the patients'

ongoing clinical pain. It is worth noting, however, that expectations and emotional feelings appear to be an important way of differentiating experiences during placebo and nocebo interventions.

4.5. Conclusion

The present study shows that placebo effects can be obtained in both ongoing and evoked neuropathic pain, and these results are consistent with antihyperalgesia and reduced central sensitization. It further suggests that expectation during placebo intervention coexist with emotional feelings about treatments, and it will be important to further investigate this aspect. In the present study, nocebo effects were less evident in neuropathic pain patients. These findings have important implications for clinical practice and research. As patients' experiences of openly administered treatments appear to be influenced by expectations and coexisting emotions arising in the treatment setting, health care providers may influence this experience by actively optimizing patients' expectations and emotional feelings without deception.

Conflict of interest statement

The authors report no conflict of interest.

Acknowledgments

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Appendix 1

Experiential method

The experiential method was developed by Barrell and Price for the study of human experience by means of basic principles of phenomenology and psychometric methods [3], [47] and [50]. The purpose of the method is to understand the meaning of a given phenomenon in our experience and to preserve the vitality of the experience as it happens. Individuals are trained to notice brief episodes of direct experience, such as emotions and pain, and to report these experiences without interpretations and explanations. The experiential reports are qualitatively sampled to determine the common elements within the experience and to characterize the interrelationships among them. They are also scaled using psychometric methods to investigate whether the reports of direct experience support quantitative data [50]. Hence, the approach represents an integration of experiential variables and traditionally used methods in natural science.

Experiential method as applied in this study

Immediately after the treatment was administrated and before it had taken effect, the patients were asked to relive their experience of the placebo and nocebo interventions, respectively. They were told that we were only interested in their inner experience as it naturally occurred and not their interpretation or explanation of it. Because the patients were not trained in characterizing their inner experiences, we

applied a simplified version of the experiential method [24] and [49]. We specifically asked the patients to quantitatively rate their emotional feelings on the M-VAS and to qualitatively describe these types of phenomenal experience in a few words. As part of the introduction to the study, the patients were carefully informed about the meaning of their experiences and emotional feelings, and examples were provided. Emotional feelings were explained as both positive and negative emotions, which are generally localized in the body (eg, sadness, joy, and fear) but may also be experienced as mental events (eg, "I was hoping that the cream would help me") [23] and [24]. Before the experiment, the patients were asked to relieve their experience in the waiting room 2 min before they were called in for the study in order to familiarize them with the method. The enclosed sheet was used for the sampling of the patients' experiences.

Data analysis

The patients did not have extensive training in differentiating between their thoughts and emotions, and therefore elements of thoughts were present in the emotional categories. The quantitative data were analyzed as means and standard deviations based on the M-VAS ratings, whereas the qualitative data were analyzed as the most frequently reported emotions. It was further calculated how many patients described the most frequently reported types of experience. As patients' experience of a placebo and nocebo effect occurred in the open condition, it seemed most meaningful to compare the experiential experiences in the 2 open conditions.

Your experience

Brief description of what you experienced during the *last 2 minutes* (from when you received the treatment and until now):

_____

Please mark the following categories in case they describe your experience. If you select one category (by a vertical line), please rate the intensity of the category on the line. The mark must indicate your experienced intensity of the category, for example, positive emotions may vary from "no positive emotional feeling" (=0) to "the most intense positive emotional feeling imaginable" (=10). Please also describe your experience of the marked category in a few words.

Positive emotional feelings

____ 0_____ 10

Description of positive emotional feelings:

_____

Negative emotional feelings

____ 0_____10

Description of negative emotional feelings:

_____

None of the categories match my experience _____

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