Research Paper

PAIN

OPEN

Learning mechanisms in nocebo hyperalgesia: the role of conditioning and extinction processes

Mia Athina Thomaidou[a,b,*], Dieuwke Swaantje Veldhuijzen[a,b], Kaya Joanne Peerdeman[a,b], Naomi Zoë Sifra Wiebing[a], Joseph Sullivan Blythe[a,b], Andrea Walbruga Maria Evers[a,b,c]

Abstract

Nocebo hyperalgesia is a clinically relevant phenomenon and may be formed as a result of associative learning, implemented by classical conditioning. This study explored for the first time distinct nocebo conditioning methods and their consequences for nocebo attenuation methods. Healthy participants (N = 140) were recruited and randomized to the following nocebo hyperalgesia induction groups: conditioning with continuous reinforcement (CRF), conditioning with partial reinforcement (PRF), and a sham-conditioning control group. In the attenuation phase, counterconditioning was compared with extinction. During induction, participants experienced increased thermal pain in 100% of nocebo trials in the CRF groups, while in only 70% of nocebo trials in the PRF groups. During evocation, pain stimulation was equivalent across all trials. During attenuation, pain stimulation was decreased on nocebo trials relative to control trials for the counterconditioning groups, while pain remained equivalent across all trials for the extinction groups. Results showed that both PRF and CRF significantly induced nocebo hyperalgesia, but CRF was a more potent nocebo induction method, as compared to PRF. Counterconditioning was more effective than extinction in attenuating nocebo hyperalgesia. Neither CRF nor PRF resulted in resistance to extinction. However, compared with CRF, conditioning with PRF resulted in more resistance to counterconditioning. These findings demonstrate that the more ambiguous learning method of PRF can induce nocebo hyperalgesia and may potentially explain the treatment resistance and chronification seen in clinical practice. Further research is required to establish whether attenuation with counterconditioning is generalizable to clinical settings.

Keywords: Pain, Nocebo effects, Nocebo hyperalgesia, Partial reinforcement, Continuous reinforcement, Conditioning, Counterconditioning, Extinction, Associative learning

1. Introduction

It has been demonstrated that negative expectations regarding treatment outcomes may aggravate pain symptoms,[3,22,34,41] a phenomenon termed nocebo hyperalgesia.[3,10] In experimental research, nocebo hyperalgesia is defined as a significant increase in pain after a nocebo treatment, relative to no-treatment or a control treatment. Negative expectations may enhance aversive side effects[31] or produce deleterious effects on pain recovery.[15] Classical conditioning is an important underlying mechanism of nocebo hyperalgesia.[7,13,20] In conditioning paradigms, the pairing of a conditioned stimulus (eg, an inert treatment) with an unconditioned stimulus (eg, surreptitiously increased pain) leads to a learned association.[5,12] As a result of this learned association, an inert treatment can evoke increases in perceived pain.[20]

Most nocebo studies induce hyperalgesia by use of conditioning with continuous reinforcement (CRF) (100% pairing of conditioned stimulus and unconditioned stimulus). In a more ambiguous type of conditioning with partial reinforcement (PRF), stimuli are paired in less than 100% of trials; thus, the contingency between pain and an inert nocebo treatment is more variable. Partial reinforcement is of particular clinical interest due to its variable nature, which resembles the more ambiguous and inconsistent learning that may occur in clinical settings.[4] Partial reinforcement conditioning has been successfully used in fear research[37] and was recently also implemented in nocebo research.[18] Colagiuri et al.[18] compared continuous and PRF schedules and found that nocebo hyperalgesia can be induced through PRF. In addition, Colagiuri et al.[18] investigated the consistent finding from fear studies that PRF conditioning shows more resistance to extinction than CRF.[1,37,45] In contrast to findings in other fields of research,[37] extinction was unsuccessful in attenuating nocebo hyperalgesia irrespective of the conditioning schedule.[18] This indicated that, once established, nocebo hyperalgesia may be especially resistant to extinction, a relevant finding for chronic pain conditions, where learned effects may persist and not become extinct.

If extinction is unsuccessful in attenuating these learned effects, a more active approach may be needed to attenuate

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Health, Medical and Neuropsychology Unit, Leiden University, Leiden, the Netherlands, [b] Leiden Institute for Brain & Cognition, Leiden, the Netherlands, [c] Department of Psychiatry, Leiden University Medical Center, Leiden, the Netherlands

**Corresponding author. Address: Health, Medical and Neuropsychology Unit, Leiden University, Wassenaarseweg 52, 2333 AK Leiden, the Netherlands. Tel.: 071 527 3008. E-mail address: a.m.thomaidou@fsw.leidenuniv.nl (M.A. Thomaidou).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 161 (2020) 1597–1608

http://dx.doi.org/10.1097/j.pain.0000000000001861

nocebo hyperalgesia. A promising novel method is counterconditioning. Unlike in extinction, during counterconditioning, the negative stimulus is replaced by a more positive stimulus.[24] Counterconditioning has recently been successful in different fields.[26,30] However, despite its potential as a basis for the treatment of nocebo-augmented pain,[9] it remains unclear whether counterconditioning would be an effective intervention for the attenuation of learned nocebo responses.

In this study, we compared 2 nocebo induction methods, conditioning with partial and CRF. Furthermore, we examined the consequences of partial vs continuous conditioning for the attenuation of nocebo hyperalgesia via counterconditioning or extinction. We expected to reproduce earlier findings that PRF would successfully induce nocebo hyperalgesia and that compared to CRF, PRF conditioning would lead to more resistance to extinction. We furthermore examined counterconditioning as a potential attenuation method for nocebo hyperalgesia. The implementation of novel, clinically relevant learning-based methods for investigating nocebo hyperalgesia is an important step towards eventually diminishing nocebo effects in clinical settings.

2. Materials and methods

2.1. Participants

One hundred and forty participants were enrolled in this study. The required sample size for the primary analysis was calculated based on a previous similar nocebo study.[18] The analysis was conducted in G*power 3.1[23] for a mixed-model analysis of variance (ANOVA). The effect size was $f = 0.26$, alpha error probability was set at $\alpha = 0.05$, desired power was set at 0.95, and the correlation for repeated measures was set at 0.05 (because of the subjectivity and high variability expected in pain ratings). According to the total sample size indicated, we planned for 140 participants to be enrolled, of which a total of 122 participants were included in the study. This sample size for the primary hypothesis is similar to previous studies examining subtle between-group differences such as conditioning with PRF or anxiety correlates.[2,18] The main groups were split into half for the purposes of some of the secondary analyses in this two-by-two design, resulting in subgroups of 24 to 25 participants, a sample size that has been used in previous nocebo studies that yielded significant results with good effect sizes.[9,17,19]

Participants were required to be between 18 and 35 years old and have a good understanding of the Dutch language as well as (corrected to) normal vision and hearing. Exclusion criteria were serious medical or psychiatric conditions, pregnancy, painful health conditions experienced in the past 6 months, and pain or use of analgesic medication at the time of testing. Participants who were determined to have too high of a threshold for pain upon their visit to the department (ie, when thermode maximum temperatures were not sufficient to induce at least moderate pain) were also excluded from the study. All participants were asked to refrain from alcohol and caffeine consumption, as well as the use of drugs and analgesic medication, in the 12 hours before the testing appointment. Participants were recruited through flyers, social media advertisements, and the online recruitment website Sona (Sona Systems, Tallinn, Estonia). Study participation involved a 2-hour testing appointment at a research laboratory of the Faculty of Social and Behavioral Sciences of Leiden University, the Netherlands. All participants provided written informed consent before the start of the experiment. After completing the experiment, all participants were reimbursed by either cash or study credits for their participation. This study was approved by the Leiden University Psychology Research Ethics Committee (CEP18-0816/318) and preregistered on ClinicalTrials.gov (NCT03793790).

2.2. Design

This study used a randomized, two-by-two design, with an additional control group (**Fig. 1**). A randomization list was created by an independent researcher, and participants were randomly allocated to 1 of 5 groups only after the calibration procedure was complete, so to reduce any risk of bias. All participants underwent a two-phase study design of which each phase consisted of 2 parts. The induction phase (phase 1) comprised an induction part in which associations were learned and an evocation part in which learned associations were tested. The attenuation phase (phase 2) comprised either counterconditioning or extinction to examine the attenuation of the learned responses and a second evocation part to test whether learned associations were still present. Group 1 received conditioning with PRF and counterconditioning. Group 2 received conditioning with PRF and extinction. Group 3 received conditioning with CRF and counterconditioning. Group 4 received conditioning with CRF and extinction. Group 5 (the sham control group) received sham conditioning and also underwent "extinction" to keep the length and procedures of the experiment identical for all participants.

2.3. Thermal pain application

Thermal pain stimuli were delivered to the nondominant volar forearm using a Thermal Sensory Analyzer with a 3 × 3-cm thermode probe (TSA-II; Medoc Advanced Medical Systems, Ramat Yishai, Israel). Throughout the experiment, pain intensities were rated on a pain numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable).

2.3.1. Sensory thresholds

To test warmth and pain threshold levels, heat stimuli were applied, and participants were asked to indicate the first moment at which they perceived warmth and the first moment they perceived pain. The average of 3 warmth detection values and 3 heat pain detection values were determined as the threshold values for warmth and pain, respectively. This method followed published standardized and protocolled procedures.[38]

2.3.2. Pain calibration protocol and administered stimuli

Pain calibrations were conducted to select the temperatures that would be used to induce low, moderate, and high pain in phases 1 and 2. The calibrations were individually tailored, based on the NRS ratings of 42 heat stimuli of varying intensities, as well as participants' bodily and facial reactions to pain stimuli. For the calibration procedure as well as throughout the experiment, each stimulus was initiated from a 32°C baseline, increased to a target temperature, and presented for 4 seconds, excluding a ramp-up rate of 8°C per second and a return rate of 8°C per second. The interstimulus interval was 8 seconds. Median temperatures consistently rated and experienced as NRS 2 to 3 were selected and used to induce low pain, median temperatures rated as NRS 4 to 6 were used to induce moderate pain, and median temperatures rated as NRS 7 to 8 were used to induce high pain. During induction and during attenuation, 15 nocebo and 15 control stimuli were administered in pseudorandom order, so that no 3 stimuli of the same type were administered in a row. During each of the 2 evocations, 5 nocebo and 5 control stimuli were

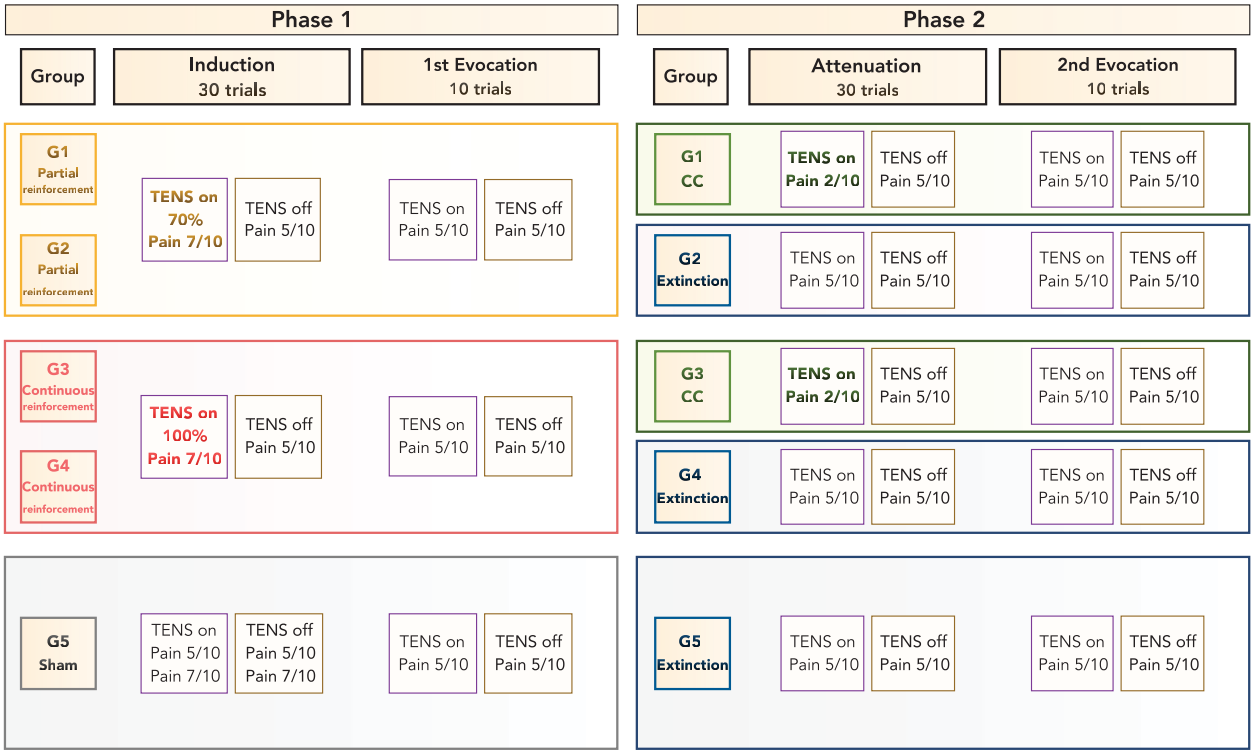

Figure 1. Illustration of the experimental design. Participants were randomly allocated to 1 of 5 groups: partial reinforcement-counterconditioning (G1); partial reinforcement-extinction (G2); continuous reinforcement-counterconditioning (G3); continuous reinforcement-extinction (G4); and sham (G5). During partial reinforcement (G1 and G2) participants received high pain in 70% of nocebo trials and moderate pain in 30% of nocebo trials. The sham group (G5) received high pain in 50% of nocebo trials and in 50% of control trials. In the attenuation phase, during counterconditioning (G1 and G3), participants received low pain in all nocebo trials, whereas during extinction (G2 and G4), participants received moderate pain for both the nocebo and the control trials. The sham group was not expected to present a nocebo response but underwent extinction only to keep the procedure equal in length for all participants. CC, counterconditioning; TENS, transcutaneous electrical nerve stimulation.

administered in pseudorandom order. To reduce habituation to heat pain, the thermode was moved twice (midway through phases 1 and 2) to a more proximal site on the same arm.

2.4. Nocebo treatment

A commercial Transcutaneous Electrical Nerve Stimulation (TENS) device (Beurer EM 80) was used to serve as the nocebo treatment in the procedure. Negative suggestions were used to create expectations regarding the pain-enhancing effects of the device (Appendix 1, available online as supplemental digital content at http://links.lww.com/PAIN/A978). Two TENS electrodes were placed in a diagonal line on the ball of the hand and the inner elbow. Before the start of the induction phase, participants underwent a short mock calibration procedure during which they felt a light electrical pulse of the TENS. This pulse was delivered to increase the believability of the nocebo verbal suggestion. Participants were told that the device was called "ENS," to avoid that participants would recognize or associate any previous experience with this device. The device was not actually activated during the conditioning procedure, but messages displayed on a computer screen through E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA) signaled the sham activation and deactivation of the TENS device during nocebo and control trials, respectively.

As part of the nocebo suggestions, participants read an information sheet (see Appendix 1, available online as supplemental digital content at http://links.lww.com/PAIN/A978), displayed on a tablet, containing (sham) information regarding the supposed effects of the TENS treatment. During nocebo induction, negative suggestions indicated to all participants that when the messages "ENS on" (in purple font; nocebo cue) and "ENS off" (in yellow font; control cue) were displayed, their pain would be aggravated or not altered, respectively.

Sham TENS activation was paired to surreptitiously increased pain stimulation during nocebo trials, while moderate pain was delivered during control trials during the induction phase. For the PRF groups, the activation of the TENS device was paired with high pain stimuli in only 70% of nocebo trials (unpaired trials were pseudorandomized to achieve an approximately even distribution throughout the induction phase). The CRF groups received high pain stimuli in 100% of nocebo trials. The control group received sham conditioning, where TENS activation was not consistently paired to the intensity of pain stimuli, but rather, this group received high pain in 50% of nocebo trials and in 50% of control trials. In the first evocation phase, all pain stimuli were applied at moderate intensity, preceded by the nocebo and control cues, to evoke conditioned responses. Increased pain reports for the first nocebo trial as compared to the first control trial in this phase indicated nocebo hyperalgesia. During attenuation, the counterconditioning groups received surreptitiously decreased pain stimulations during TENS activation, while TENS deactivation was still paired to moderate pain inductions. During extinction, participants continued being exposed to pain stimuli at only moderate intensity preceded by the nocebo and control cues. During the second evocation phase, all pain stimuli were applied at moderate intensity, preceded by the nocebo and control visual cues, to test whether nocebo responses were diminished after attenuation.

2.5. Questionnaires

Four questionnaires were used to measure baseline differences in psychological characteristics. Total scores were used for all questionnaires. A short State Anxiety version of the State-Trait Anxiety Inventory (STAI-S)[28,42] was used once before the start (STAI state pre) and once after the end of the experiment (STAI state post). Scores on this questionnaire range from 20 to 80, with higher scores indicating higher state anxiety. Cronbach's alpha in this study were 0.77 (pre) and 0.74 (post). The STAI, Trait version (STAI-T)[42] was also used, with scores also ranging from 20 to 80 and higher scores indicating higher trait anxiety. Cronbach's alpha was 0.83 in this study. The Pain Catastrophizing Scale[43] was used to assess catastrophizing thoughts related to pain, with scores ranging from 0 to 52, where higher scores indicate more frequent catastrophizing thoughts. Cronbach's alpha was 0.87 in this study. The revised Life Orientation Test (LOT-R)[40] was used to measure dispositional optimism vs pessimism. Scores on this questionnaire range from 0 to 24, with higher scores indicating higher optimism. Cronbach's alpha was 0.69 in this study. Participants were also asked to rate their tiredness on a 0 to 10 NRS scale from "not at all" to "very much." Moreover, a screening questionnaire containing demographic and health questions was used to screen participants for inclusion in the study. At the end of the experiment, participants completed an exit questionnaire containing manipulation check questions assessing pain expectations (rated on the pain NRS), how much they trusted the experimenters, and how honest they believed the experimenters were (rated on a 0-10 NRS from "not at all" to "very much"). The exit questionnaire also assessed whether participants believed the cover story or was aware of the real purpose of the experiment (ie, the manipulation of expectations or use of conditioning). All questionnaires, as well as a debriefing from, were displayed on a tablet using web-based survey software (Qualtrics, Provo, Utah).

2.6. Experimental procedure

On the day of the appointment, participants were first provided with information about the experiment and were asked to provide written-informed consent. Then, participants completed the screening and the psychological questionnaires. After this, they read the information sheet about the (sham) pain-enhancing effects of the TENS device. Warmth and pain threshold levels were then tested, and individual pain stimuli were calibrated. Participants then underwent nocebo induction through conditioning with PRF, CRF, or sham conditioning. The first evocation phase where nocebo responses were tested then followed. Subsequently, participants underwent nocebo attenuation, through either counterconditioning or extinction. A second evocation phase then followed, where the presence of nocebo responses after attenuation was tested. After the end of the experiment, participants were asked to complete the exit questionnaire. Then, a debriefing was conducted, and participants were reimbursed for their participation.

2.7. Statistical analyses

All data were analyzed by use of SPSS 23.0 (IBM Corp, Armonk, NY). A one-way ANOVA was conducted between all groups for mean scores on each of the questionnaires and the tiredness rating, to determine whether any personal characteristics could have influenced the results. One-way ANOVAs were also used to assess between-group differences in state anxiety, trust in the experimenter, and pain expectations, as assessed at the end of the experiment and in temperatures used to induce pain and the NRS pain scores throughout the experiment. As these analyses involved multiple between-group comparisons, the threshold for significance was set at $P < 0.01$. Next, mean values and SDs were calculated for warmth and pain thresholds.

2.7.1. Primary and secondary outcome measures

The magnitude of reported nocebo hyperalgesia (primary outcome measure) was measured within-subject and was defined as the difference in pain ratings for the first nocebo trial compared with the first control trial, during first evocation. The reduction of induced nocebo hyperalgesia after attenuation was measured as the change in reported pain for the first nocebo trials between the first and second evocation. The first trials of each testing phase were selected since previous studies indicate the effect to be clearest in those trials.[8,18] Difference scores between nocebo and control trials as mentioned above were only used for manipulation checks and descriptive purposes (**Tables 1 and 2**). To conduct mixed-model ANOVA, the assumptions of normality, independence, and homogeneity of the variances were checked. Unless otherwise stated, the threshold for significance was set at $P < 0.05$. As an effect size measure, partial eta-squared (η_p^2) was calculated for analyses of primary and secondary outcomes, with η_p^2 of 0.01 considered small, 0.06 considered medium, and 0.14 considered large.[16,36]

2.7.2. Nocebo hyperalgesia induction

First, to examine whether a significant nocebo response was present after nocebo induction, a 3 × 2 mixed-model ANOVA was used, treating induction group as the between-subject factor with 3 levels (PRF, CRF, or sham) and magnitude of the nocebo response as a within-subject factor with 2 levels (first nocebo trial and first control trial). As this primary analysis involved multiple between-group comparisons, a conservative Bonferroni correction was applied, and the threshold for significance was set at $P < 0.01$. Where a significant interaction effect would be detected, planned contrasts would be analyzed (using 2 × 2 mixed-model ANOVAs) between each of the pairs of experimental groups.

2.7.3. Nocebo hyperalgesia attenuation

To test the hypothesis that counterconditioning would be more effective than extinction in attenuating nocebo hyperalgesia, a 2 × 2 mixed-model ANOVA was performed with attenuation group as the between-subject factor with 2 levels (counterconditioning and extinction) and the nocebo reduction as the within-subject factor with 2 levels (first nocebo trial of the first evocation phase before attenuation and first nocebo trial of the second evocation phase after attenuation).

2.7.4. Resistance to extinction

To test the hypothesis that conditioning with PRF would lead to a more durable nocebo effect as compared to conditioning with CRF, we explored resistance to extinction. A 2 × 2 mixed-model ANOVA was performed with the induction group as between-subject factor with 2 levels (PRF extinction and CRF extinction) and the nocebo response as the within-subject factor with 2 levels (first nocebo trial of the first evocation phase before attenuation and first nocebo trial of the second evocation phase after attenuation). After this, 2 repeated-measures ANOVAs were conducted with the nocebo response as the within-subject factor

Table 1

Group mean values and SDs, as well as between-group *P* values, for questionnaire scores, calibrated temperatures, reported pain, and postexperimental manipulation-check questions.

	1 PRF − CC		2 PRF − extinction		3 CRF − CC		4 CRF − extinction		5 sham		All groups		*P*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Preassessment													
STAI Trait	40.2	8.0	37.2	5.7	37.6	8.1	36.8	7.4	38.8	6.6	38.1	7.2	0.45
STAI State pre	50.8	24.4	52.7	23.1	48.6	25.1	44.3	18.6	44.2	16.6	48.1	21.7	0.56
PCS	13.6	8.1	12.9	6.6	11.9	5.4	13.8	6.8	13.4	8.0	13.1	7.0	0.90
LOT-R optimism	16.9	3.3	14.8	3.5	17.2	2.6	16.1	2.9	15.1	3.4	16.0	3.3	0.33
Tiredness (NRS)	3.4	2.0	2.9	2.1	3.4	2.3	3.9	2.5	3.3	2.3	3.4	2.3	0.60
Calibrations													
Low °C	45.0	0.8	45.1	1.1	45.5	1.1	45.0	0.9	45.0	0.5	45.1	0.9	0.31
Moderate °C	46.8	0.7	47.0	0.8	47.0	0.8	46.7	1.1	46.9	0.7	46.9	0.8	0.61
High °C	48.4	0.5	48.6	0.7	48.8	0.6	48.5	0.8	48.5	0.5	48.6	0.6	0.31
Induction													
Nocebo trials NRS*	6.6	1.7	6.2	1.7	7.3	1.5	6.6	1.6	5.8	1.6	6.5	1.7	0.03
Control trials NRS	4.6	1.8	4.4	1.8	4.8	1.6	3.7	1.5	5.7	1.7	4.6	1.8	0.002†
Attenuation													
Nocebo trials NRS	3.2	2.0	4.4	2.0	2.6	1.4	3.8	2.0	4.0	2.1	3.6	2.0	0.01‡
Control trials NRS*	4.5	2.0	3.9	2.1	4.1	1.7	3.2	2.0	3.9	1.9	3.9	2.0	0.31
Postassessment													
STAI State post	32.3	8.7	29.8	7.5	31.6	10.6	31.3	8.3	31.1	5.8	31.2	8.2	0.87
Trust in researcher (NRS)	8.5	2.1	8.6	1.7	8.7	1.8	8.6	1.7	9.3	0.9	8.7	1.7	0.49
Honesty of researcher (NRS)	7.4	2.3	7.6	2.2	7.5	2.2	6.7	2.3	7.2	2.6	7.3	2.3	0.65
Pain expectation induction (NRS)	6.4	1.8	6.0	1.7	6.4	1.7	6.5	1.7	5.2	1.9	6.1	1.8	0.06
Pain expectation attenuation (NRS)	4.4	1.9	4.9	2.1	3.6	2.2	4.3	1.9	4.1	1.8	4.2	2.0	0.22

Alpha set at 0.01. The NRS was always 0 to 10.

* Excluding 1 trial from each phase immediately after thermode was moved (trial 21 of each phase).

† Significant difference was driven by the administration of different types of trials in the sham group.

‡ Significant difference was driven by the administration of lower pain for nocebo trials in the counterconditioning group.

°C, temperature used in degrees celsius; CC, counterconditioning group; CRF, continuous reinforcement group; PRF, partial reinforcement group; LOT-R, Life Orientation Scale-Revised; NRS, numeric rating scale score; PCS, Pain Catastrophizing Scale; STAI, Spielberger State Anxiety Inventory.

with 2 levels (as described above), to test whether extinction significantly reduced the magnitude of nocebo hyperalgesia within the PRF group and within the CRF group.

2.7.5. Manipulation check for the time course of extinction

Because of the unique attenuation paradigm in the experiment, we implemented a design that applied 10 evocation trials that were essentially extinction trials, before the start of the 30 attenuation trials. In our paradigm, 30 induction trials were followed by 10 evocation trials, which in turn were followed by 30 extinction trials. Evocation trials, however, are identical to extinction trials. This exposed participants to a longer extinction time (ie, essentially 40 trials), as compared to the 30 induction trials. To verify that any extinction or resistance effects were not present after an equal number of induction and extinction trials, we analyzed the 30th trial after the start of evocation. A 2 × 2 mixed-model ANOVA was performed with the induction group as between-subject factor with 2 levels (PRF extinction and CRF extinction) and the nocebo response during extinction as the within-subject factor with 2 levels (20th nocebo extinction trial and 21st control extinction trial).

2.7.6. Resistance to counterconditioning

It was also assessed whether a resistance effect to counterconditioning was present. A 2 × 2 mixed-model ANOVA was performed with induction group as the between-subject factor with 2 levels (PRF-counterconditioning and CRF-counterconditioning) and nocebo response as the within-subject factor with 2 levels (first nocebo trial of the first evocation phase before attenuation and first nocebo trial of the second evocation phase after attenuation). After this, 2 repeated-measures ANOVAs were conducted with the nocebo response as the within-subject factor with 2 levels (as described above), to test whether counterconditioning significantly reduced the magnitude of nocebo hyperalgesia within the PRF group and within the CRF group.

2.7.7. Time course of attenuation

To explore the time course and slopes of attenuation, a line graph was plotted. Mean NRS pain ratings were plotted for the nocebo trials after the end of nocebo induction, in the PRF-counterconditioning group, the PRF-extinction group, the CRF-counterconditioning group, and the CRF-extinction group.

2.7.8. Manipulation check for control trials

We ran manipulation checks to examine any effect of changes in control trial ratings on the reduction of nocebo responses after attenuation. This was performed to assure that the effects of attenuation were not driven by changes in the ratings of control trials (TENS off), which could confound the results, for example, if between-group differences were detected, or in the case that general sensitization or habituation to pain had occurred. First, an analysis of the control trial ratings in all groups was performed. A 5 × 2 mixed-model ANOVA was performed with group as the between-subject factor with 5 levels (groups 1, 2, 3, 4, and 5) and

the first control trial rating of each evocation phase as the within-subject factor with 2 levels (control preattenuation and control postattenuation). As this analysis involved multiple between-group comparisons, a conservative Bonferroni correction was applied, and the threshold for significance was set at $P < 0.01$. A nonsignificant result would indicate that the control trials did not yield significant changes, confirming that they did not affect the within-subject results of the analyses. Furthermore, we conducted a 2 × 2 mixed-model ANOVA between the attenuation groups (counterconditioning and extinction) and the preattenuation to postattenuation difference score between nocebo and control trials. In this way, we examined the reduction in the magnitude of nocebo hyperalgesia from preattenuation to postattenuation, by directly comparing control trials with nocebo trials.

2.7.9. Questionnaires

Finally, we studied the relationship of nocebo hyperalgesia and anxiety, pain catastrophizing, and optimism. Scores obtained through the 4 psychological questionnaires were analyzed using correlation analyses, to explore whether any of these psychological characteristics were associated with the magnitude of induced nocebo hyperalgesia.

3. Results

3.1. Participants, temperatures, and pain ratings

A total of 140 participants were enrolled in this study (118 females and 22 males). Six participants were excluded because of technical difficulties or noise disturbance in the laboratory, 4 participants were unable to complete the study due to sleepiness, intense anxiety, or inability to follow instructions, 3 participants were excluded because of exhibiting a too-high threshold for pain (ie, not reaching a moderate pain rating during calibrations), 2 participants were excluded because of fulfilling one of the health-related exclusion criteria (namely, experiencing moderate head or neck pain at the time of testing), 2 participants were excluded because of knowing the purpose of the experiment as assessed in the postassessment survey, and 1 participant was excluded because of insufficient understanding of Dutch. A total of 122 participants were included in the final analyses, 102 females and 20 males. Randomization across the 5 groups resulted in a total of 25 participants in group 1 (PRF-counterconditioning), 24 participants in group 2 (PRF extinction), 24 participants in group 3 (CRF-counterconditioning), 24 participants in group 4 (CRF extinction), and 25 participants in group 5 (sham). Participants were stratified for gender, so that each group contained 5 male participants.

Descriptive data of the questionnaire scores, temperature levels, and pain ratings are listed in **Table 1**. One-way ANOVAs indicated that there were no significant between-group differences in the mean scores on any of the psychological questionnaires. The mean warmth detection threshold across all participants was 33.5°C (SD = 0.5), and the mean pain threshold was 42.3°C (SD = 2.9). The results of a one-way ANOVA indicated that there were no significant group differences in the mean temperatures selected to induce low, moderate, and high pain. A one-way ANOVA detected a significant group difference in the ratings of the control trials of the induction phase; however, when the analysis was performed again with the sham group removed, it was revealed that this difference was merely driven by the sham group, where half of the control trials were purposely paired with high pain stimulation. Despite moving the thermode several times during the experiment to avoid habituation to the heat stimuli, an overall decrease in pain ratings over time was observed (**Table 1**, conditioning and attenuation rows).

3.2. Normality checks

The ANOVA assumptions of normality, independence, and homogeneity of the variances were checked. A nonsignificant Shapiro–Wilk test and histograms of standardized residuals indicated a normal distribution of the data. Within- and between-group independence was established by randomization into groups. Homogeneity of variances was tested through a Levene's test, which indicated nonsignificant results, thereby confirming homogeneity of variance in the data.

3.3. Nocebo hyperalgesia induction

The mean magnitudes of reported nocebo hyperalgesia after induction are listed in **Table 2**. A 3 × 2 mixed-model ANOVA was conducted to establish whether there was a significant difference in the magnitude of induced nocebo hyperalgesia between PRF, CRF, and sham. The analysis revealed a significant group by trial interaction between the 3 induction groups and the magnitude of nocebo responses ($F(2,119) = 20.75$, $P < 0.001$, $\eta_p^2 = 0.26$). **Figure 2** illustrates the differences in pain ratings for the first nocebo trial and the first control trial of the first evocation, across all 3 groups. Three 2 × 2 mixed-model ANOVA-planned analyses revealed a significant interaction between the PRF and sham group and the magnitude of nocebo responses ($F(1,72) = 20.58$, $P < 0.001$, $\eta_p^2 = 0.22$), between the CRF and sham group and the magnitude of nocebo responses ($F(1,71) = 45.22$, $P < 0.001$, $\eta_p^2 = 0.39$), and between the PRF and CRF groups and the magnitude of nocebo responses ($F(1,95) = 7.28$, $P = 0.008$, $\eta_p^2 = 0.07$). These results indicated that conditioning with PRF and with CRF were both effective in inducing significant nocebo responses, with CRF producing a significantly larger nocebo response as compared to PRF.

3.4. Attenuated nocebo hyperalgesia

3.4.1. Counterconditioning vs extinction

The mean reduction and mean magnitudes of reported nocebo hyperalgesia after attenuation are listed in **Table 2**. To examine whether counterconditioning was more effective than extinction in attenuating the induced nocebo responses, a 2 × 2 mixed-model ANOVA was conducted. The analysis revealed a significant interaction between the counterconditioning and extinction groups and the reduction of nocebo responses ($F(1,95) = 6.51$, $P = 0.012$, $\eta_p^2 = 0.06$), indicating significantly higher efficacy of counterconditioning compared with extinction. **Figure 3** illustrates the differences in pain ratings for the first nocebo trial of the first evocation and the first nocebo trial of the second evocation, between the counterconditioning and extinction groups.

3.4.2. Resistance to extinction

The mean reduction and mean magnitudes of reported nocebo hyperalgesia after extinction are listed in **Table 2**. We conducted a 2 × 2 mixed-model ANOVA to examine whether conditioning with PRF resulted in nocebo hyperalgesia that was more resistant to extinction, as compared to conditioning with CRF. A non-significant interaction effect showed no significant difference in resistance to extinction between conditioning with PRF and CRF ($F(1,46) = 0.63$, $P = 0.43$, $\eta_p^2 = 0.01$). **Figure 4** illustrates

Table 2

Group mean values and SDs for the magnitude of reported nocebo hyperalgesia after induction and attenuation, as well as for the reduction of nocebo hyperalgesia after attenuation.

Phase 1			Phase 2							
Induction group	Nocebo magnitude		Attenuation group	Nocebo magnitude		Nocebo reduction		Induction − attenuation group	Nocebo magnitude		Nocebo reduction	
	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD
PRF	0.9	1.0	CC	−0.6	1.2	1.8	1.7	PRF − CC	−0.2	1.1	1.2	1.8
PRF								PRF – Ext	0.3	0.6	0.6	1.0
CRF	1.5	1.1	Extinction	0.3	0.6	0.9	1.1	CRF − CC	−1.0	1.2	2.3	1.6
CRF								CRF – Ext	0.3	0.6	1.3	1.1
Sham	−0.02	0.2										

Scores are reported on a 0 to 10 pain numeric rating scale. Magnitudes of nocebo hyperalgesia are shown here as the difference between the first control and first nocebo trial of each evocation phase. Reduction is shown by calculating the difference in the magnitude of nocebo hyperalgesia before and after attenuation.
CRF, continuous reinforcement; CC, counterconditioning; Ext, Extinction; PRF, partial reinforcement.

differences in pain ratings for the first nocebo trial of the first evocation and the first nocebo trial of the second evocation, between the PRF-extinction group and the CRF-extinction group. Furthermore, 2 repeated-measures ANOVAs showed a significant effect of trial type (first nocebo evocation trial preattenuation, first nocebo evocation trial postattenuation) in the PRF group ($F(1,23) = 5.26$, $P = 0.03$, $\eta_p^2 = 0.19$) and the CRF group ($F(1,23) = 10.39$, $P = 0.004$, $\eta_p^2 = 0.31$), indicating that extinction significantly reduced nocebo responses in both groups.

3.5. Manipulation check for the time course of extinction

To verify that resistance to extinction was not present at an earlier stage during attenuation, we analyzed the 20th attenuation trial; however, again, no resistance to extinction was shown. When the 30th trial after the first trial of evocation was used instead of the 30th trial after the start of attenuation, a 2 × 2 mixed-model ANOVA showed no significant difference in resistance to extinction between conditioning with PRF vs CRF ($F(1,46) = 0.61$, $P = 0.44$, $\eta_p^2 = 0.01$).

3.5.1. Resistance to counterconditioning

The mean reduction and mean magnitude of reported nocebo hyperalgesia after counterconditioning are listed in **Table 2**. We conducted a 2 × 2 mixed-model ANOVA to examine whether conditioning with PRF resulted in nocebo hyperalgesia that was

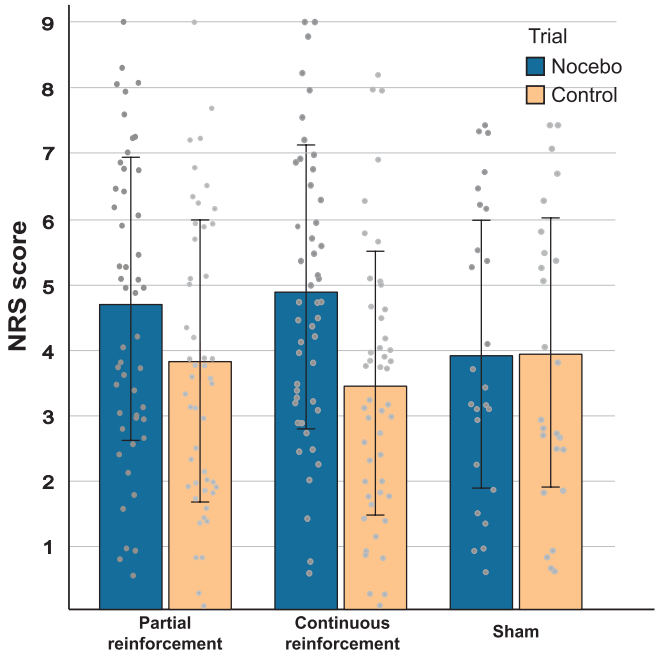

Figure 2. Numeric rating scale pain ratings for the first nocebo and the first control trial of the first evocation. Mean numeric rating scale (NRS) pain ratings and SDs are depicted across all groups (N = 122). Dots represent the (jittered) individual data points. In both the partial reinforcement and the continuous reinforcement groups, evocation pain reports during nocebo trials were significantly higher than pain reports during control trials. Sham conditioning, as expected, did not induce nocebo hyperalgesia. Conditioning with partial reinforcement yielded a significantly smaller nocebo effect than conditioning with continuous reinforcement.

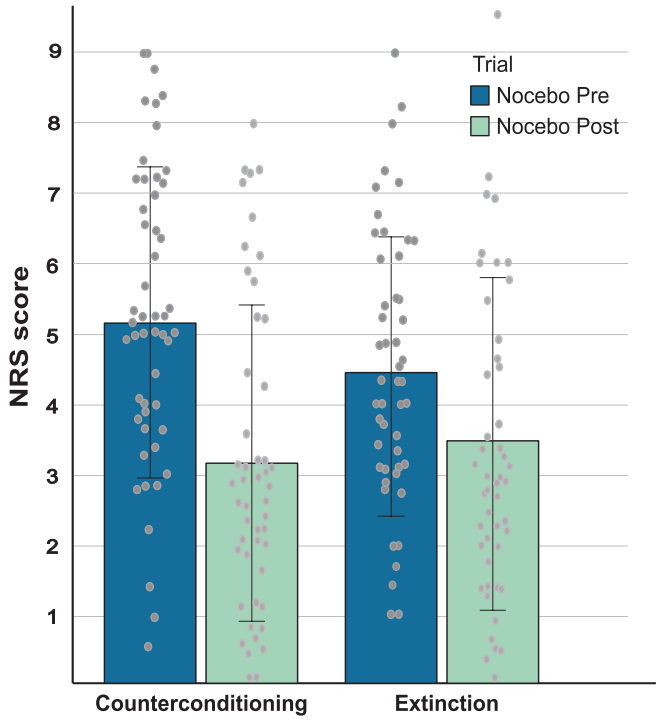

Figure 3. Comparison of nocebo magnitudes after counterconditioning and extinction. Differences in mean numeric rating scale (NRS) pain ratings and SDs between the attenuation groups (N = 97) are depicted. Dots represent the (jittered) individual data points. Differences between the first nocebo trial of the first evocation (Nocebo Pre) and the first nocebo trial of the second evocation (Nocebo Post) illustrate the significant reduction of nocebo hyperalgesia achieved by both methods. Attenuation with counterconditioning was significantly more effective in diminishing nocebo responses.

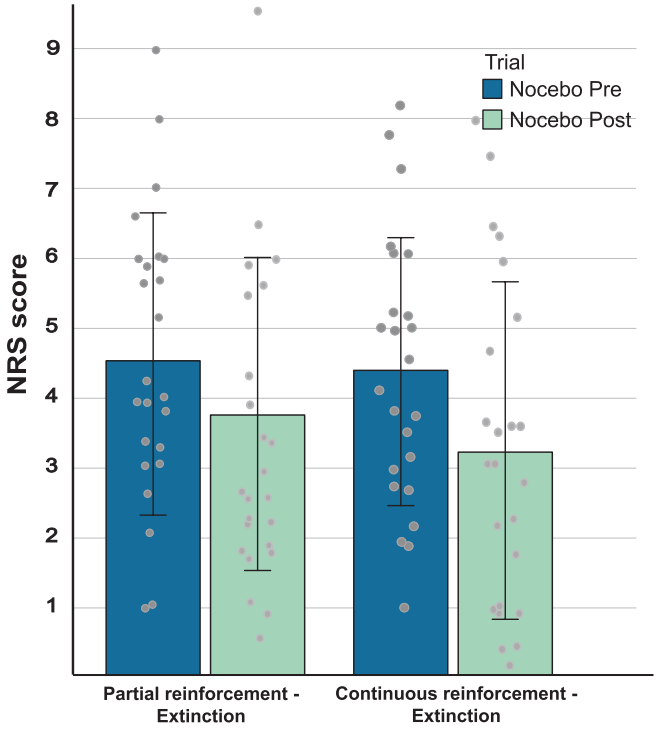

Figure 4. Comparison of nocebo magnitudes after extinction, between the partial reinforcement and continuous reinforcement. Differences in mean numeric rating scale (NRS) pain ratings and SDs between the partial reinforcement-extinction group and the continuous reinforcement-extinction group (N = 48) are depicted. Dots represent the (jittered) individual data points. The direction of the difference between the first nocebo trial of the first evocation (Nocebo Pre) and the first nocebo trial of the second evocation (Nocebo Post) pointed towards partial reinforcement resulting in a more durable nocebo response, compared with continuous reinforcement; however, this difference did not reach significance.

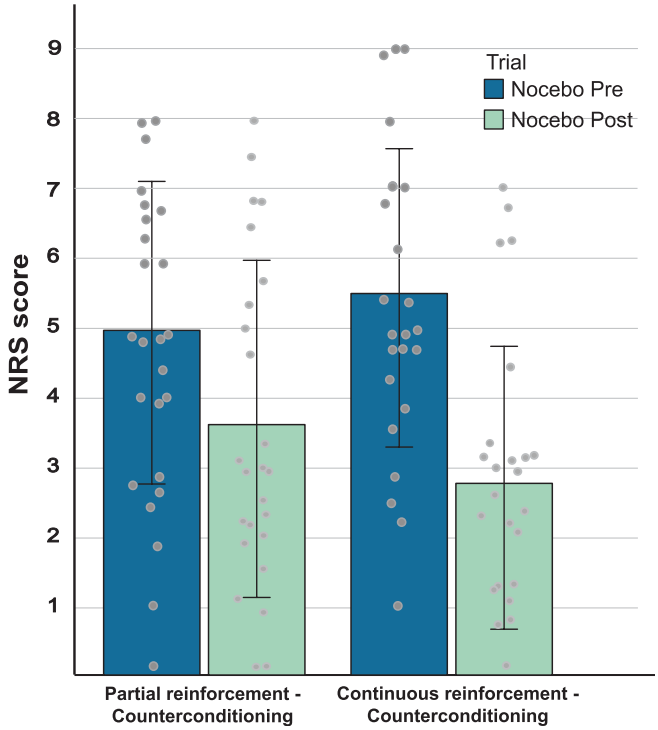

Figure 5. Comparison of nocebo magnitudes after counterconditioning, between the partial reinforcement and continuous reinforcement. Differences in mean numeric rating scale (NRS) pain ratings and SDs between the partial reinforcement-counterconditioning group and the continuous reinforcement-counterconditioning group (N = 49) are depicted. Dots represent the (jittered) individual data points. The difference between the first nocebo trial of the first evocation (Nocebo Pre) and the first nocebo trial of the second evocation (Nocebo Post) indicated that partial reinforcement induced a nocebo response that was significantly more resistant to counterconditioning, as compared to nocebo induction with continuous reinforcement.

more resistant to counterconditioning, as compared to conditioning with CRF. The analyses showed a significant difference in the resistance to counterconditioning between conditioning with PRF vs CRF ($F(1,47) = 4.99$, $P = 0.03$, $\eta_p^2 = 0.09$). **Figure 5** illustrates the differences in pain ratings for the first nocebo trial of the first evocation and the first nocebo trial of the second evocation, between the PRF-counterconditioning group and the CRF-counterconditioning group. This finding indicated that PRF leads to more resistance to counterconditioning than CRF. Furthermore, 2 repeated-measures ANOVAs showed a significant effect of trial type (first nocebo evocation trial before attenuation and first nocebo evocation trial after attenuation) in the PRF group ($F(1,24) = 15.96$, $P = 0.001$, $\eta_p^2 = 0.39$) and the CRF group ($F(1,23) = 27.65$, $P < 0.001$, $\eta_p^2 = 0.54$), indicating that counterconditioning significantly reduced nocebo responses in both groups.

3.5.2. Time course of attenuation

To explore the time course and slopes of attenuation, a line graph was plotted. **Figure 6** displays the time course of attenuation between all 4 active groups, from the start of the first evocation and throughout the attenuation phase. During attenuation, because of the counterconditioning groups receiving lower pain stimulations than the extinction groups, the nocebo trial NRS scores of the counterconditioning groups were visibly lower. It is also visible that this persisted as a learned effect, at the start of the second evocation, when all groups received moderate pain. This reduced nocebo response illustrates the higher effectiveness of counterconditioning in diminishing the previously induced nocebo hyperalgesia. In addition, the attenuation slopes illustrate that participants in the PRF-extinction and PRF-counterconditioning groups consistently provided higher pain ratings than participants in the corresponding CRF groups, despite the fact that they were receiving pain stimulations of the same intensity (low pain in the counterconditioning and moderate pain in the extinction groups). This points to a tendency for resistance to attenuation after PRF as compared to after CRF, already during learning. However, during the second evocation, the difference between PRF and CRF did not reach significance in the extinction groups.

3.5.3. Manipulation check for the control trials

Finally, as a first manipulation check, it was assessed whether changes in the ratings of the control trials influenced the results of the attenuation phase. A 5 × 2 mixed-model ANOVA revealed no significant differences in the NRS pain ratings for control trials before and after attenuation ($F(4,117) = 0.62$, $P = 0.64$, $\eta_p^2 = 0.02$). This result indicates that the control trials did not yield significant changes from preattenuation to postattenuation and that the reduction in nocebo hyperalgesia was in fact driven by changes in nocebo responses before and after attenuation. To further examine whether control trials could have affected the attenuation results, a 2 × 2 mixed-model ANOVA was conducted with the attenuation group as the between-subject factor and the magnitude of nocebo hyperalgesia as the within-subject factor

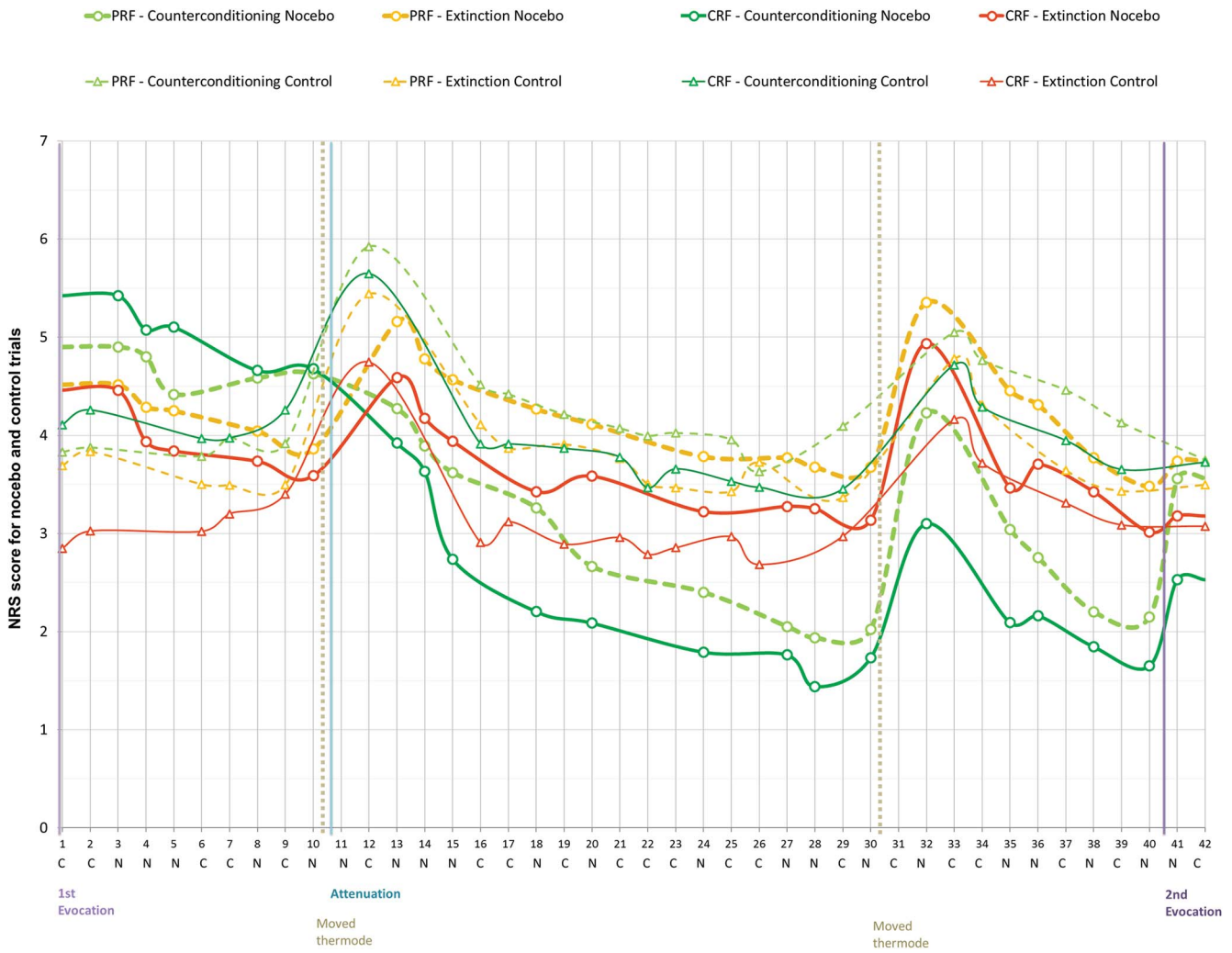

Figure 6. Pain ratings for nocebo and control trials after the end of induction, across all active conditioning groups. Numeric rating scale (NRS) pain ratings during nocebo and control trials illustrate the time course of attenuation, for the partial reinforcement (PRF)-counterconditioning group, partial reinforcement (PRF)-extinction group, continuous reinforcement (CRF)-counterconditioning group, and continuous reinforcement (CRF)-extinction group. Circles on the thick lines, over the letters N on the x axis, represent the nocebo trials and triangles on the thin lines, over the letters C on the x axis, represent the control trials. The dotted vertical lines indicate the thermode moving point, after which pain ratings suddenly peak due to placing the thermode on a new location on the arm. During the evocations, all pain stimuli were administered at the same intensity (only the first trials of the second evocation are included in this figure, for clarity, as only these were included in the analyses). It is visible that the counterconditioning groups (green lines) received lower pain stimulations during attenuation. Notably, participants in the PRF-extinction and PRF-counterconditioning groups (dashed lines) consistently provided higher pain ratings than participants in the corresponding CRF groups (unbroken lines), despite the fact that they were receiving pain stimulations of the same intensity. Control trials did not yield significant differences from before to after attenuation.

with 2 levels (nocebo-control difference score before attenuation and nocebo-control difference score after attenuation). The analysis revealed a significant interaction between the counterconditioning and extinction groups and the reduction of nocebo responses ($F(1,95) = 6.87$, $P = 0.009$, $\eta_p^2 = 0.07$), indicating significantly higher efficacy of counterconditioning compared with extinction (**Fig. 6**), also when the control trials where included in the analysis. **Figure 6** depicts time-series data for the evocation and attenuation phases and illustrates that control trials did not yield changes from preattenuation to postattenuation that would impact nocebo trials or inferences about the attenuation of nocebo effects.

3.6. Questionnaires

Spearman's rank-order correlation analyses indicated that there was no significant relationship between the magnitude of nocebo hyperalgesia in the active groups (ie, excluding the sham conditioning group) and trait or state anxiety, pain catastrophizing, or optimism scores (STAI trait: $r = -0.07$, $P = 0.49$; STAI state pre: $r = -0.06$, $P = 0.55$; STAI state post: $r = -0.13$, $P = 0.19$; Pain Catastrophizing Scale: $r = -0.06$, $P = 0.54$; LOT-R: $r = -0.05$, $P = 0.59$).

4. Discussion

The current study compared distinct and novel methods for the induction and attenuation of nocebo hyperalgesia. We demonstrated that PRF conditioning was sufficient to induce nocebo hyperalgesia, as was CRF conditioning. Furthermore, we showed that counterconditioning is a more potent method than extinction for the attenuation of nocebo hyperalgesia. Interestingly, our results also showed that, despite pain ratings remaining consistently higher in the PRF group compared with the CRF

group during extinction, this difference did not reach significance and resistance to extinction after conditioning with PRF was not observed. Importantly, we found that while counterconditioning was sufficient to attenuate nocebo responses irrespective of induction method, nocebo hyperalgesia was significantly more resistant to counterconditioning when induced through partial, as compared to CRF. These findings have a number of implications related to experimental models and clinical practice.

The finding that conditioning with PRF is, albeit less potent than CRF, sufficient to induce nocebo hyperalgesia and is in line with previous research by Colagiuri et al.[18] Reproducing these results and reaffirming the potency of the more ambiguous partial learning method has important theoretical and clinical implications. Conditioning with learning schedules that provide more variable contingencies bears a closer resemblance to what nocebo theories postulate regarding the ambiguity of learning and negative suggestions in clinical contexts.[18,22] Using a more ecologically valid paradigm can have a crucial impact on our understanding of how and why nocebo hyperalgesia may present in pain patients.

Studying the attenuation of nocebo hyperalgesia provides insights into the mechanisms that may contribute to the chronification of pain. Although in this study extinction was sufficient to attenuate nocebo hyperalgesia, counterconditioning was a more powerful intervention, reversing nocebo responses into an effect resembling placebo responses. Counterconditioning being more powerful than extinction can be explained by counterconditioning involving a paradigm that bears closer resemblance to successful exposure therapy techniques. For example, for the treatment of phobias[32,39] and anxiety,[35] the initial association between the aversive stimulus and fear becomes attenuated through a procedure involving the removal of fear or threat.[33] However, in the current study, extinction entailed a reduction of pain to the levels of control (moderate) pain stimulations, rather than the entire removal of these aversive stimuli. In pain paradigms, it is often impossible, both experimentally and clinically, to achieve the entire removal of the aversive stimulus during extinction. In counterconditioning, however, the painful stimuli were reduced to a level that was perceived as less unpleasant in comparison even with control pain stimulations, leading to a significantly larger reduction of nocebo responses. This is in line with findings by Meulders et al.[30] who showed that changing the valence of aversive stimuli might improve fear reduction and potentially prevent relapse. In contrast to the frequently observed lack in effectivity and durability of extinction,[6,32,44] this counterconditioning finding indicates that there may be a path for experimental therapeutics in this field to move away from traditional extinction paradigms and attempt more active ways of minimizing learned responses.

Nocebo hyperalgesia has consistently been found to be resistant to extinction,[17,18,27] which may indicate an important mechanism of pain chronification. Moreover, research exploring the learning correlates and effectivity of conditioning with PRF has previously shown that ambiguous learning schedules produce durable conditioned effects,[1,4,37,45] including previous PRF research on nocebo[18] and placebo effects.[4] In this study, we did not find a statistically significantly larger resistance to extinction after partial, as compared to CRF. Extinction trends pointed towards PRF resulting in more durable nocebo responses compared with CRF, as illustrated in **Figures 4 and 6**; however, this difference was not significant. Moreover, it was observed that during attenuation, pain reports in the PRF group did remain consistently higher than those in the CRF group (**Fig. 6**), despite the fact that after induction, PRF produced a significantly weaker nocebo response than CRF. The effectivity of extinction even after PRF could be explained by the fact that exposure to extinction was longer than exposure to nocebo induction, when considering the first evocation phase. It is worth pointing out, however, that in real-world contexts, patients may be exposed to shorter periods during which nocebo hyperalgesia is acquired and longer periods of extinction. As such, the current model provides novel evidence that nocebo hyperalgesia can be extinguished over prolonged exposure to extinction, even after PRF learning.

Interestingly, a PRF resistance effect was found when attenuation involved counterconditioning. Counterconditioning was still successful in attenuating nocebo effects after conditioning with PRF; however, counterconditioning was observed to be substantially more effective after conditioning with CRF (**Table 2** and **Fig. 5**). Importantly, this effect was observed despite the fact that PRF had resulted in a significantly weaker nocebo response. This counterconditioning-specific resistance effect could be attributed to negativity bias (ie, the tendency to attend to or remember negative experiences over neutral or positive experiences[11,25,29]). According to this theory, when provided with inconsistent positive and negative information about the same stimulus, individuals are more likely to retain the negative information.[14] A negativity bias may have taken place after the ambiguous information provided to participants in the PRF group and the formation of mixed expectations regarding the activation of the nocebo treatment. The PRF-counterconditioning group was exposed to a wider range of negative and positive suggestions and associations. It is possible that during the final evocation, the negative treatment associations were retained over the positive ones. A resistance to the attenuation with counterconditioning may thus be in line with previous literature about this type of negativity bias.[14] This effect may be of important clinical relevance because it could shed light on the etiology of pain chronification after exposure to inconsistent, mixed information and experiences. In turn, however, this means that the potency of counterconditioning after ambiguous and variable learning remains uncertain. Gaining a better understanding of the learning mechanisms underlying the process of rewriting negative associations can be crucial for the further utilization of counterconditioning as a therapeutic approach to nocebo hyperalgesia.

One limitation of this study, as mentioned earlier, was the discrepancy in the length of induction and attenuation, which may explain why nocebo responses were not resistant to extinction. Colagiuri et al.[18] only applied extinction allowed the paradigm to comprise an equal number of induction and attenuation trials. In the current study, because of our aim of comparing counterconditioning and extinction, a longer evocation phase was preferred before the start of attenuation. Participants were thus exposed to longer extinction, as compared to induction. Nevertheless, in clinical contexts and chronic pain, unequal lengths of exposure to suggestions, learning, and extinction may also exist. Future research should address the role that the time course of induction and attenuation may play. Another limitation of this study and a common obstacle in nocebo studies was related to the nocebo suggestions. In this novel counterconditioning approach, the suggestions had to indicate that the same treatment could increase but also decrease pain sensitivity. The suggestion that pain would be decreased by the same device that previously increased pain sensitivity could have been confusing to participants. In future research, nocebo suggestions can be optimized by comparing different cover stories and instructions because these are crucial for influencing expectations. A common

limitation in the learning process of extinction is the return of the conditioned response, such as fear, after the passing of time.[21] The current study did not examine this effect, which is believed to result from competing learned effects and deficits in inhibitory learning and more specifically deficits in the neural regulation needed during extinction.[21] Future counterconditioning experiments could shed light on whether—and under which conditions—such a reinstatement could take place after counterconditioning. Further research into the effectivity and durability of counterconditioning is necessary to establish whether this method can provide a basis for clinical interventions targeting nocebo effects. Finally, controlling for variables in our sample such as caffeine intake and age range or limiting our sample to higher education students may have created potential confounding variables. In future studies, it would be important to allow for more variance in the participant sample and to collect and check data related to variables such as caffeine intake, age, and education. Overall, future studies should collect and analyze manipulation check data to see whether and how different variables can influence study outcomes.

This study implemented a complete, clinically relevant model of nocebo hyperalgesia, from acquisition to attenuation. The findings reproduced previous evidence of ambiguous and variable learning being sufficient to induce nocebo hyperalgesia and that this type of induction method may be more resistant to treatments. This study also provided evidence that counterconditioning is a powerful method for the attenuation of nocebo hyperalgesia. Counterconditioning, however, may be less potent in attenuating effects that have been induced by more ambiguous learning and should therefore undergo further assessment within ecologically valid experimental models, in healthy and patient populations.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgments

The authors thank Aleksandrina Skvortsova for her valuable insights during the setup of this study. The authors also thank Dr Julian D. Karch for his help with methodological and statistical aspects of this study. This work was supported by a VICI grant from the Netherlands Organization for Scientific Research (NWO; grant number 45316004) and a European Research Council Consolidator Grant (ERC-2013-CoG-617700), granted to A. Evers.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A978.

Article history:
Received 8 November 2019
Received in revised form 21 February 2020
Accepted 2 March 2020
Available online 5 March 2020

References

[1] Amsel A, Wong P, Traupmann K. Short-term and long-term factors in extinction and durable persistence. J Exp Psychol 1971;90:90–5.
[2] Aslaksen PM, Lyby PS. Fear of pain potentiates nocebo hyperalgesia. J Pain Res 2015;8:703–10.
[3] Atlas LY, Wager TD. How expectations shape pain. Neurosci Lett 2012; 520:140–8.
[4] Au Yeung ST, Colagiuri B, Lovibond PF, Colloca L. Partial reinforcement, extinction, and placebo analgesia. PAIN 2014;155:1110–17.
[5] Bąbel P, Bajcar EA, Adamczyk W, Kicman P, Lisińska N, Świder K, Colloca L. Classical conditioning without verbal suggestions elicits placebo analgesia and nocebo hyperalgesia. PLoS One 2017;12:e0181856.
[6] Baeyens F, Díaz E, Ruiz G. Resistance to extinction of human evaluative conditioning using a between-subjects design. Cogn Emot 2005;19: 245–68.
[7] Bajcar EA, Wiercioch-Kuzianik K, Adamczyk WM, Bąbel P. To experience or to be informed? Classical conditioning induces nocebo hyperalgesia even when placebo analgesia is verbally suggested—results of a preliminary study. Pain Med 2020;21:548–60.
[8] Bartels DJP, van Laarhoven AIM, Haverkamp EA, Wilder-Smith OH, Donders ART, van Middendorp H, van de Kerkhof PCM, Evers AWM. Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. PLoS One 2014;9:e91727.
[9] Bartels DJP, van Laarhoven AIM, Stroo M, Hijne K, Peerdeman KJ, Donders ART, van de Kerkhof PCM, Evers AWM. Minimizing nocebo effects by conditioning with verbal suggestion: a randomized clinical trial in healthy humans. PLoS One 2017;12:e0182959.
[10] Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: unraveling the mechanisms of the nocebo effect. Neuroscience 2007; 147:260–71.
[11] Berntson GG, Cacioppo JT. The neuroevolution of motivation. In: Shah JY, Gardner WL, editors. Handbook of motivation science. New York: The Guilford Press, 2008. p. 191.
[12] Blythe JS, Peerdeman KJ, Veldhuijzen DS, van Laarhoven AIM, Evers AWM. Placebo and nocebo effects on itch. Itch 2019;4:e27.
[13] Bräscher A-KK, Kleinböhl D, Hölzl R, Becker S. Differential classical conditioning of the nocebo effect: increasing heat-pain perception without verbal suggestions. Front Psychol 2017;8:1–12.
[14] Cacioppo JT, Cacioppo S, Gollan JK. The negativity bias: conceptualization, quantification, and individual differences. Behav Brain Sci 2014;37:309–10.
[15] Chavarria V, Vian J, Pereira C, Data-Franco J, Fernandes BS, Berk M, Dodd S. The placebo and nocebo phenomena: their clinical management and impact on treatment outcomes. Clin Ther 2017;39:477–86.
[16] Cohen J. A power primer. Psychol Bull 1992;112:155–9.
[17] Colagiuri B, Quinn VF. Autonomic arousal as a mechanism of the persistence of nocebo hyperalgesia. J Pain 2018;19:476–86.
[18] Colagiuri B, Quinn VF, Colloca L. Nocebo hyperalgesia, partial reinforcement, and extinction. J Pain 2015;16:995–1004.
[19] Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F. How the number of learning trials affects placebo and nocebo responses. PAIN 2010;151: 430–9.
[20] Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. PAIN 2008;136:211–18.
[21] Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B. Maximizing exposure therapy: an inhibitory learning approach. Behav Res Ther 2014; 58:10–23.
[22] Evers AWM, Colloca L, Blease C, Annoni M, Atlas LY, Benedetti F, Bingel U, Büchel C, Carvalho C, Colagiuri B, Crum AJ, Enck P, Gaab J, Geers AL, Howick J, Jensen KB, Kirsch I, Meissner K, Napadow V, Peerdeman KJ, Raz A, Rief W, Vase L, Wager TD, Wampold BE, Weimer K, Wiech K, Kaptchuk TJ, Klinger R, Kelley JM. Implications of placebo and nocebo effects for clinical practice: expert consensus. Psychother Psychosom 2018;87:204–10.
[23] Faul F, Erdfelder E, Lang AG. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–91.
[24] Hofmann W, De Houwer J, Perugini M, Baeyens F, Crombez G. Evaluative conditioning in humans: a meta-analysis. Psychol Bull 2010; 136:390–421.
[25] Ito TA, Larsen JT, Smith NK, Cacioppo JT. Negative information weighs more heavily on the brain: the negativity bias in evaluative categorizations. J Pers Soc Psychol 1998;75:887–900.
[26] Kerkhof I, Vansteenwegen D, Baeyens F, Hermans D. Counterconditioning: an effective technique for changing conditioned preferences. Exp Psychol 2011;58:31–8.
[27] Manaï M, van Middendorp H, Veldhuijzen DS, Huizinga TWJ, Evers AWM. How to prevent, minimize, or extinguish nocebo effects in pain. PAIN Rep 2019;4:e699.
[28] Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol 1992;31:301–6.

[29] McCracken LM. "Attention" to pain in persons with chronic pain: a behavioral approach. Behav Ther 1997;28:271–84.
[30] Meulders A, Karsdorp PA, Claes N, Vlaeyen JWS. Comparing counterconditioning and extinction as methods to reduce fear of movement-related pain. J Pain 2015;16:1353–65.
[31] Mitsikostas DD. Nocebo in headaches: implications for clinical practice and trial design. Curr Neurol Neurosci Rep 2012;12:132–7.
[32] Monfils MH, Cowansage KK, Klann E, LeDoux JE. Extinction-reconsolidation boundaries: key to persistent attenuation of fear memories. Science 2009; 324:951–5.
[33] Ohman A, Mineka S. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. Psychol Rev 2001;108:483–522.
[34] Reicherts P, Gerdes ABM, Pauli P, Wieser MJ. Psychological placebo and nocebo effects on pain rely on expectation and previous experience. J Pain 2016;17:203–14.
[35] Reinecke A, Waldenmaier L, Cooper MJ, Harmer CJ. Changes in automatic threat processing precede and predict clinical changes with exposure-based cognitive-behavior therapy for panic disorder. Biol Psychiatry 2013;73:1064–70.
[36] Richardson JTE. Eta squared and partial eta squared as measures of effect size in educational research. Educ Res Rev 2011;6:135–47.
[37] Robbins D. Partial reinforcement: A selective review of the alleyway literature since 1960. American Psychological Association, 1971. Available at: https://insights.ovid.com/plbul/197112000/00006823-197112000-00005. Accessed August 16, 2019.
[38] Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede R-D. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006;10:77–88.
[39] Rowe MK, Craske MG. Effects of varied-stimulus exposure training on fear reduction and return of fear. Behav Res Ther 1998;36:719–34.
[40] Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol 1994;67: 1063–78.
[41] Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JKK. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. Arch Gen Psychiatry 2008;65:220–31.
[42] Spielberger C, Gorsuch R, Lushene P, Vagg P, Jacobs A. Manual for the State-Trait Anxiety Inventory STAI (Form Y) ("Self-Evaluation Questionnaire"). Man State-Trait Anxiety Invent STAI. Palo Alto: Consulting Psychologists Press, Inc, 1983:4–6.
[43] Sullivan MJL, Bishop SR, Pivik J The Pain Catastrophizing Scale: development and validation. Psychol Assess 1995;7:524–32.
[44] VanElzakker MB, Dahlgren KM, Davis CF, Dubois S, Shin LM. From Pavlov to PTSD: the extinction of conditioned fear in rodents, humans, and anxiety disorders. Neurobiol Learn Mem 2014;113: 3–18.
[45] Weiner I, Bercovitz H, Lubow RE, Feldon J. The abolition of the partial reinforcement extinction effect (PREE) by amphetamine. Psychopharmacology (Berl) 1985;86:318–23.