Optimizing placebo effects in medical contexts: utilizing learning theories and exploring communication strategies

Smits, R.M.

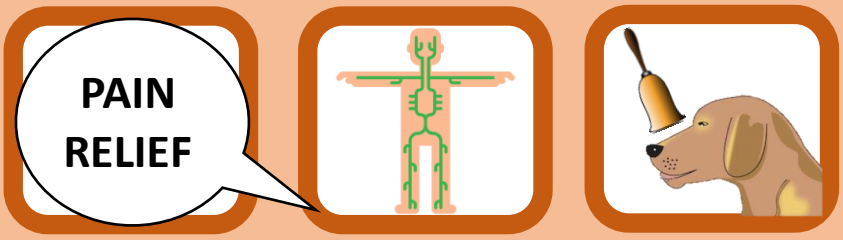
How you gonna win when you ain't right within.
- Hill, L. (Lauryn). N. (1998). Doo Wop (That Thing).
On *The Miseducation of Lauryn Hill.*

6. Inducing open-label placebo analgesia in a randomized trial with healthy controls: combining conditioning principles and instructional learning.

Under review for publication

Rosanne M. Smits1,2,3*, Dieuwke S. Veldhuijzen1,2,3, and Andrea W. M. Evers1,2,3,4,5

[1]Health, Medical and Neuropsychology unit, Leiden University, Leiden, The Netherlands; [2]Pediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, Utrecht, The Netherlands; [3]Leiden Institute for Brain and Cognition (LIBC), Leiden, The Netherlands; [4]Medical Delta Professor Healthy Society, Leiden University, Technical University Delft, & Erasmus University; [5]Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands.



Abstract

Recent developments in clinical research have demonstrated placebo analgesia with patients being aware of placebo administration, termed open-label placebo (OLP). Few studies have found OLP effects in experimental settings with healthy volunteers. This study aimed to examine OLP analgesic effects by combining conditioning and instructional learning principles in a well-validated pain conditioning paradigm. Healthy participants (N=88) were randomized to an OLP group, deceptive placebo group (DP), or a control group. Participants from the OLP and DP groups were exposed to a two-phased (acquisition and evocation phase) conditioning procedure with heat stimulations of low and moderate intensities, paired with ON and OFF messages of a placebo sham device, respectively. Placebo effects were reinforced by positive verbal suggestions in both placebo groups. Additionally, the OLP group received a placebo reveal based on newly developed placebo information strategies. The control group received sham conditioning without positive verbal suggestions and a placebo rationale. Results indicated a significant difference in pain reduction for the OLP and control group (p = .026), and no difference between the OLP and DP group (p = .734). Future research into the use of OLP analgesia is recommended due to its ethical advantages and potential for clinical application. This study was preregistered in the Dutch Trial Register: Trial NL8220.

Perspective: This article examines placebo analgesia without the use of deception (open-label placebo) in an experimental setting by combining learning principles conditioning and instructional learning. Results of this study can guide future research in using a transparent form of placebo analgesia and aid its potential use to clinical practice.

Keywords: Pain, Open-label placebos, Conditioning, Thermal heat pain, Instructional learning

INTRODUCTION

The influence of placebo effects in treatments has recently gained more attention because of their potential to optimize therapeutic outcomes(1, 2). Underlying learning mechanisms that steer placebo effects, such as classical conditioning and instructional learning (e.g. expectations induced by verbal suggestions) have been extensively studied, particularly in experimental pain conditioning paradigms(3, 4). In such paradigms, experimentally induced pain (e.g. heat pain) can be reduced by conditioned placebo analgesia, where pairings of a sham (placebo) treatment (conditioned stimulus; CS) and pain analgesia (unconditioned stimulus; US) form a conditioned placebo analgesic response (conditioned response; CR)(5, 6). Moreover, positive verbal suggestions about pain relief may have an additive effect on conditioned placebo analgesia, and can potentially increase the magnitude of placebo effects combined with conditioning principles(7-9). However, not all studies have found support for these combined effects, possibly because the exact content of the verbal suggestions to induce analgesic effects is not clearly understood yet(10, 11).

Recently, new developments in placebo research have taken place, where placebo effects have been induced in a more transparent way, called open-label placebos (OLP). With the use of OLPs, placebo administration is fully disclosed in contrast to placebo use in its traditional way, which is often used in a deceptive context. Due to this ethical benefit, OLP use advances its potential application in clinical practice(11-17). Several studies with patient samples have demonstrated that OLPs can exceed the efficacy of no treatment or treatment as usual control groups and in some studies even show similar effects compared to deceptive placebos(7, 13-20). In experimental settings with healthy volunteers however, the effects of OLP over a control group have not been studied much(15, 16, 21). To gain more insights in the potential efficacy of OLP and its underlying mechanisms, it would be useful to further examine the effects of OLP in experimental context.

Moreover, the instructions provided about the therapeutic benefits of placebo effects, the placebo rationale, may play an important role in generating and harnessing expectations about OLP effects(12, 16). In a previous study from our research group, a broad range of placebo explanations was compared with the aim to optimize instructions for OLPs. This study showed that explanations focusing on

positive expectations and neurobiological underpinnings were most preferred as placebo instructions and may be integrated in OLP research(22).

The present study incorporates two important learning mechanisms involved in placebo effects, namely classical conditioning and instructional learning. Conditioning principles are applied with a well-validated conditioning paradigm, and instructional learning is incorporated through positive verbal suggestions, thereby distinguishing from previous experimental OLP studies that mainly used instructional learning(15, 16, 21). Moreover, this study uses a OLP rationale based on newly developed placebo instructions(22). The primary aim of this study is to compare the analgesic effects of OLPs with a control group. It was hypothesized that placebo effects will be higher in the OLP group that underwent a conditioning procedure with OLP verbal suggestions than in the control group. The secondary aim of this study was to compare OLP and deceptive placebo (DP) analgesic effects. We hypothesized that both groups would demonstrate similar effects in placebo analgesic effects, as demonstrated in previous literature(12-14, 16). For exploratory purposes we also investigated all three groups simultaneously, and the role of state anxiety(6), dispositional optimism(3, 23), and pain expectations as these factors have been previously associated with placebo effects.

METHODS

Study design

A randomized, single-blind, controlled trial was conducted between October 2019 and April 2020 at the Faculty of Social and Behavioural Sciences, Department of Health, Medical and Neuropsychology at Leiden University. Participants were randomly assigned to one of three groups: OLP (N = 31), DP (N = 29), or a control group (N = 28). The study design consisted of two phases: an acquisition phase in which an association between a placebo treatment (CS) and pain analgesia (UCS) was formed, and an evocation phase to measure the extent of this learned association (CR; conditioned placebo analgesia) (see **Figure 1**). Ethical approval was received by the Psychology Research Ethics Committee (CEP19-1010/497). The study was preregistered in the Dutch Trial Register: Trial NL8220.

Study population

Eighty-eight healthy participants were enrolled in this study and recruited through flyers, social media advertisements, and an online recruitment website Sona (Sona Systems, Tallinn, Estonia). The sample size was calculated with G*Power 3.1(24) and based on the primary comparison between the OLP and control groups (no treatment or treatment as usual) derived from previous studies, such as chronic low back pain (N=83; d = 0.53(13)), irritable bowel syndrome (N = 80; d = 0.79(14)) and fatigue in cancer survivors (N = 40; d = 0.57(25)). Our statistical power analysis was calculated for a mixed ANOVA with three groups based on the effect size described by Carvalho and colleagues of d = 0.53, indicating that a sample of 57 (19 per group) was needed to obtain a power of .95 at an alpha level of α=0.05. To be more in line with the sample sizes of previous experimental OLP studies (30 to 40 participants per group)(15, 16, 21), we increased the sample to 96 participants (32 per group; drop outs not included). Due to the global pandemic from COVID-19 we were unfortunately forced to stop the inclusions at 88 participants. However, since our sample size is much larger than initially based on the sample size calculation of Carvalho and colleagues, with a power of .95, we would be able to detect the desired effect. Based on this larger sample size of 88 participants, we would now be able to detect an effect size of d = 0.43 as calculated with G*Power(24).

Participants had to be healthy (as assessed by self-report), able to understand and speak English and were between 16 to 35 years of age. Exclusion criteria included refusal to give informed consent, severe morbidity (e.g. multiple sclerosis, heart and lung disease), suffering or have suffered from pain lasting for ≥ 6 months, serious neurological or psychiatric conditions, use of recreational drugs 1 week before participation, current use of analgesic medication, substance abuse, injuries on arms or hands, pregnancy or lactation and previous participation in similar heat pain experiments. Participants were asked one day prior to the experiment to withhold from alcohol consumption, and from nicotine and coffee consumption 3 hours before participation. Participants gave written consent before participation and were reimbursed afterwards. All participants were reimbursed with €15.00 or four course credits (for undergraduate Psychology students only).

Study procedure

Participants were invited to the lab, where two experimenters conducted the experiment and informed the participants that the study's purpose focused on the role of personality on pain perception. After signing informed consent, a screening questionnaire was filled out to assess whether inclusion criteria were met. The experimental procedure started with a calibration phase in which individualized warmth and heat pain thresholds were assessed (see section 2.5.1: Calibration phase). Once individualized heat pain temperatures for low, moderate and high pain were determined, participants were randomly assigned to the OLP, DP, or the control group. A randomization list was prepared by an independent researcher by block randomization using random sequence allocations generated by Microsoft Excel for Windows, version 2016 (Microsoft Corp, Redmund, WA). The amount of participants starting with active placebo treatment in the evocation phase was counterbalanced across the groups, and groups were stratified by gender (female/male ratio of 2:1).

After randomization, all participants were presented with a leaflet (see Supplementary material I) that contained information about the placebo treatment, which was transcutaneous electric nerve stimulation (TENS; EM 80, Beurer GmbH, Ulm, Germany) The sham device was called "ENS" in the present experiment to avoid familiarity or recognition with the device. The placebo groups read information about the scientifical evidence of the device to alleviate heat pain. Only in the control group, information and evidence about the analgesic effects of ENS were omitted and instead, the participants were told that ENS works for some people, but for others it doesn't have any effect on pain. In addition, the OLP group received a leaflet that explained how placebo effects induce pain relief by positive expectations and neurobiological processes, even when participants are aware of placebo administration (the ENS device in this case). The instructions selected in this study were based on a comprehensive comparison of different placebo instructions from a previous study (see **Table 1)**(22).

Table 1. Placebo rationale for the OLP group

Positive expectations	**Expectations** have a big impact on treatment outcomes. If you have **positive expectations**, they may develop a more positive treatment outcome and affect your pain experience in this present study. You may not only feel better from the procedure itself, but also because you expect to feel better.
Brain mechanisms	Positive expectations also affect **processes** in your body**.** When you have positive expectations, the brain produces chemicals. These chemical substances are called **neurotransmitters** and can make you feel better. Placebos can also trigger the release of neurotransmitters. In this study we will be making use of these processes to reduce pain

Note. For the OLP group, participants were also provided with information about the magnitude of placebo effects in treatments and were made aware that the (T)ENS device was switched off during the experiment to induce placebo effects. Complete leaflets from all groups can be found in Supplementary file I.

After the participants had read the information leaflet, the experimenters summarized information from the leaflets with verbal suggestions about the ENS (see **Table 2**) and a short ENS mock calibration procedure was carried out. During this mock calibration procedure, light ENS pulsations were administered and gradually decreased until participants indicated that they could not feel the pulsations anymore. The participants were told that this procedure was used to establish a suitable and effective mode below perception level, and that this mode would be saved for the entire duration of the experiment. In reality, after the demonstration of the ENS, the experimenters switched off the device and only made the OLP group aware of this. Cues on a computer screen using E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA) indicated the (sham) activation of the ENS device during the acquisition and evocation phase. In sum, the DP and OLP group followed the same procedure, but only the OLP received a placebo rationale and verbal suggestions that revealed inactivation of the sham device.

Table 2. Verbal suggestions about the placebo device (ENS) per group	
Control	"You just read how ENS works. The mode we are testing is an older technique and we don't expect this to have any effect on pain, but of course for comparison purposes we have to test this."
Deceptive placebo	"You just read how ENS can decrease pain. Through these electrodes, the device can send light electrical pulses that can affect nerve conduction. From previous research, we know it decreases pain in the majority, about 92% of the people, so when the ENS is on, you'll probably feel less pain from the heat."
Open-label placebo	"As you have read, there is mounting evidence that it may not be the device itself that causes pain reduction, but pain relief may actually be the result of placebo effects. Placebo effects can have a big impact on pain perception. To date, hundreds of studies have demonstrated that placebo effects can influence chemical processes in the body to successfully alter pain experiences. In this experiment you will see cues on the computer screen informing you to when the ENS device is turned on and off. This is when we expect the placebo effects to be experienced. In reality, the device will be switched off during the experiment but it is definitely possible for you to experience less pain because of the placebo effects induced by these cues."

After the ENS mock calibration procedure, a well-validated two-phased heat pain conditioning paradigm(26) consisting of an acquisition phase and an evocation phase was executed. During the acquisition phase, the experimental groups (OLP and DP) were presented with "ON" cues on a computer screen that signaled (sham) ENS activation, and with "OFF" cues on a computer screen that signaled ENS deactivation. The "ON" and "OFF" cues were then followed by individualized pain intensities of low and moderate pain stimulations, respectively. The control group underwent a sham conditioning procedure, in which 50% of the "ON" cues corresponded to low heat pain stimulations, and 50% of the "OFF" cues corresponded to moderate heat pain stimulations to negate the effects of conditioning. During the evocation phase, only moderate pain intensities were administered and placebo effects were measured. After the evocation phase, participants were asked to fill out psychological questionnaires, were debriefed about the initial purpose of the study, and financially compensated for their participation.

Pain assessment

Heat pain stimulations were induced by the PATHWAY model ATS (Medoc Advanced Medical System, Rimat Yishai, Israel). A 3 x 3-cm thermode with a baseline temperature of 32°C was placed on the ventral side of the participants arm with a maximum temperature of 50°C. Pain scores and expected pain scores were rated on a visual numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable). The ENS served as a placebo treatment and was attached to the ventral forearm with two self-adhesive gel electrodes. Placebo effects were measured by comparing pain ratings after the “ON” versus the “OFF” cues.

Calibration phase

First**,** warmth and heat pain thresholds were established with ascending heat stimulations where participants had to indicate the first time they felt a temperature change (warmth thresholds, *t*), and the first time they experienced pain (heat pain thresholds, *T*) according to a validated conditioning paradigm from previously published procedures(27). Both procedures were repeated three times with one practice trial. Thresholds were calculated by the mean of the three temperatures. Throughout the experiment, stimuli were presented for 4 seconds from a 32°C baseline to a maximum temperature of 50°C, and returned with 8°C per second, with an interstimulus interval of 8 seconds. Subsequently, participants received an ascending series of maximum 18 heat stimulations and were asked to rate the pain experienced on the NRS. Once the participant reached a pain score of 7 or higher, the program was stopped and the last series of the calibration phase was started, because higher pain levels were not of interest for current research purposes. In the last series, 18 heat stimulations that corresponded to low (NRS scores between 1 and 3), moderate (NRS scores between 3.5 and 5.5) and high pain (NRS scores between 6 and 8) were intermittently induced to check for the consistency of pain scores. Following this procedure, individualized median temperatures for low, moderate and high pain levels were established. For the remainder of the procedure only the low and moderate pain levels were used, but to indicate the range of heat pain levels to participants, high pain levels were also measured during the calibration phase.

Acquisition and evocation phase

During the acquisition phase, a yellow cue on the computer screen showed “ON” and was followed by an individualized temperature that corresponded to low pain intensity. A purple cue on the screen showing “OFF” was followed by an individualized temperature that corresponded to a moderate pain intensity. The colors yellow and purple were chosen based on the disassociation with pain intensities from previous literature(28). The acquisition phase consisted of ten “ON” trials and ten “OFF” trials and were presented in pseudorandom order. The length of the acquisition phase was based on previous conditioning studies that induced placebo effects with deceptive placebos and open-label placebos(5, 6, 20). To check whether expectations were successfully induced by the verbal suggestions, participants were asked about their expected pain scores after being presented with an “ON” or “OFF” cue. Pain expectations were asked 4 times during the acquisition phase (2 times after an “ON” cue, and 2 times after an “OFF” cue) and 2 times during the evocation phase (prior to an “ON” and an “OFF” cue). During the evocation phase, 6 moderate heat pain temperatures were administered, 3 trials after an “ON” cue and 3 trials after an “OFF” cue, of which the pain ratings were compared to measure placebo effects.

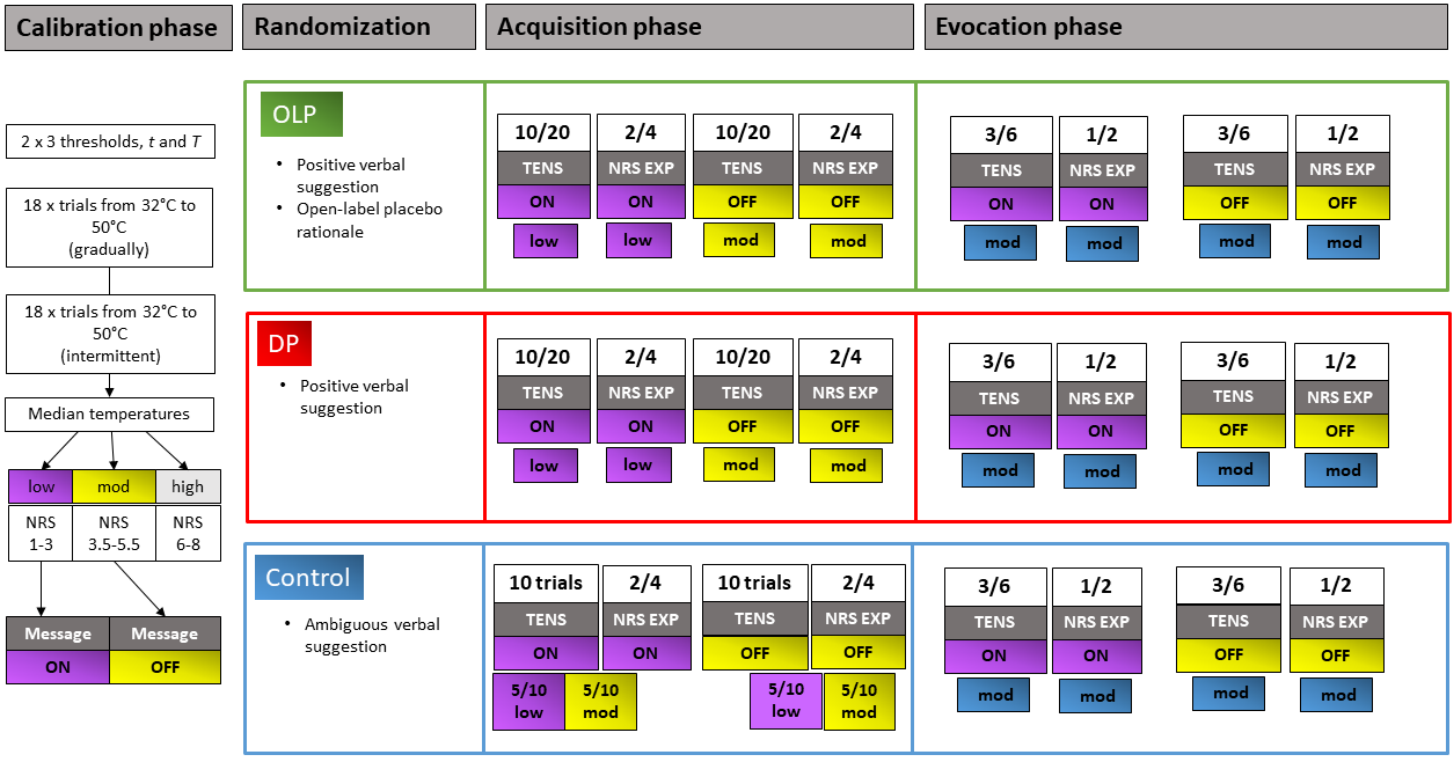


Figure 1. Experimental design. Participants were randomized to one of three groups; open-label placebo (OLP), deceptive placebo (DP), and a control group. All participants underwent the same calibration phase to establish individualized heat pain levels. The experimental groups (OLP and DP) underwent a conditioning procedure of 20 trials, with "ON" cues corresponding to low pain, and "OFF" cues to moderate pain. The control group underwent a sham conditioning procedure of 20 pseudorandomized trials, not related to "ON" or "OFF" cues. During an evocation phase all participants received 6 heat pain stimuli of moderate (mod) intensities with 3 "ON" and 3 "OFF" cues. Pain expectations were asked 4 times during the acquisition phase (twice before an "ON" cue and twice before "OFF" cues) and 2 times during the evocation phase (once before "ON" and once before "OFF"). *TENS ('ENS' in the study) = transcutaneous electric nerve stimulation (placebo device), NRS = pain scores on an numerical rating scale, NRS EXP = pain expectancy scores measured on a numerical rating scale, t = warmth thresholds, T = pain thresholds.*

Questionnaires

During the screening phase, demographic variables (age, sex, education and nationality) and pre-test state anxiety using the short 6-item version of the State-Trait Anxiety Inventory (STAI)(29) were assessed. Total scores on the STAI short version ranged from 20 to 80, with higher scores indicating higher levels of state anxiety(29). Current pain was assessed based on the NRS (0 = no pain to 10 = worst pain imaginable)(30), and expected pain was also assessed based on the NRS ("How painful do you expect the next stimuli to be from 0 to 10, based on the device being ON/OFF, with 0 = no pain to 10 = worst pain imaginable"). At the end of the evocation phase, participants filled out the STAI short version again to compare pre- and post-test levels of anxiety, and the Life Orientation Test Revised (LOT-R) consisting of 10 items was filled out to assess the personality trait optimism with total scores ranging from 0-24. Higher scores indicated higher levels of dispositional optimism(31).

Statistical analyses

Data were analyzed using IBM SPSS Statistics (version 25). To determine between-groups differences, one-way ANOVAs were conducted on the demographic and questionnaire data age, pre-test anxiety, post-test anxiety, dispositional optimism, pain expectations from the acquisition and evocation phase, thresholds, temperatures used to induce low and moderate pain, and NRS scores for low and moderate temperatures in the acquisition phase. For all analyses a significance level of <.05 was considered to be significant and post-hoc tests were conducted which were Bonferroni corrected when all three groups were compared. Group differences for categorical variables were checked with a chi-square test of independence. Assumptions were checked; tests did not indicate any violations. Partial eta squared (ηp^2) were reported for effect sizes with values of 0.01 considered as a small effect, 0.06 as a moderate effect and 0.14 as a large effect(32). Demographic and questionnaire variables that indicated significant differences between groups were additionally entered in the main analyses as covariates.

Prior to the main analysis, a manipulation check was conducted to verify whether the conditioning procedure was successful in eliciting lower pain ratings after the "ON" cues versus the "OFF" cues in the acquisition phase with a mixed ANOVA that compared averaged pain scores of the "ON" and "OFF cues at the within-subject

level and Groups at between-subject level. Furthermore, we compared all ten separate “ON” and “OFF” trials in a mixed ANOVA to explore the time course of the acquisition phase for all three groups, and explored the time course of pain expectations from the acquisition after the two “ON” and two “OFF” cues with a similar mixed ANOVA.

To answer the primary research question, namely whether placebo effects were significantly higher in the OLP group compared to the control group, planned contrasts were conducted with the OLP group versus the control group as was also pre-registered (NTR: Trial NL8220). For the main analyses, mixed ANOVAs were conducted with Cue (2 levels: first “ON” and first “OFF” trials of the evocation phase) as the within-subject factor and Group (2 levels: OLP group and control group) as the between-subject factor. For the secondary research question, the same analysis was conducted with a planned contrast for the OLP versus the DP group. As an exploratory analysis, we also conducted a mixed ANOVA with post-hoc Bonferroni corrections to compare all three groups. In addition, we repeated this last analysis with the pain ratings from all three “ON” versus “OFF” trials separately from the evocation phase to investigate the time course of placebo effects.

To explore associations between psychological measures (pre-test and post-test state anxiety, dispositional optimism, and expectations about forthcoming pain) and placebo effects, Pearson correlation analyses were conducted. For this analysis, the magnitude of the placebo effect was calculated in which both placebo groups were aggregated, by the differences in pain scores from the first trials of the test phase, after placebo activation (“ON” cues) and deactivation (“OFF” cues). Pain expectations were calculated in a similar way and computed for both the acquisition and evocation phase. In line with previous research(6, 33), significant outcomes from the correlation analysis were entered in a (multiple) regression model analyses to predict placebo responses.

RESULTS

Sample characteristics

From the 108 participants that were recruited, a total of 88 participants were enrolled (M*age* = 23, SD = 3.1, 61 females). Two participants were excluded based on not meeting the inclusion criteria (1 person due to cannabis use and 1 person due to previous participation in a study with thermal heat pain), and 18 participants were excluded after the calibration phase because of inconsistent pain scores or not being able to discriminate between distinct levels of thermal heat pain. The three groups did not significantly differ in age ($F(2,83) = .248$, $p = .781$) warmth thresholds ($F(2,83) = 2.200$, $p = .117$) pain thresholds ($F(2,83) = .732$, $p = .484$), temperatures corresponding to low pain ($F(2,85) = 1.143$, $p = .324$), NRS scores for low pain ($F(2,85) = 2.860$, $p = .063$), NRS scores for moderate pain ($F(2,85) = 2.600$, $p = .080$), temperatures corresponding to moderate pain ($F(2,85) = .942$, $p = .394$), post-test state anxiety ($F(2,83) = .276$, $p = .760$), dispositional optimism ($F(2,83) = 1.917$, $p = .154$), and pain expectations from the acquisition phase ($F(2,85) = 32.786$, $p = .191$), but groups did differ in pre-test state anxiety ($F(2,83) = 3,180$, $p = .047$) and pain expectations from the evocation phase ($F(2,85) = 4.411$, $p = .015$) which were driven by higher scores in the OLP group compared to the other groups (see **Table 3**).

Table 3. Group mean values and SDs for demographics, questionnaire scores and warmth and pain thresholds.

	OLP (N=31)		DP (N=29)		Control (N=28)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age[a]	23.0	2.9	23.0	3.6	23.6	2.7
Gender (M:F)[b]	10:21	-	9:20	-	8:20	-
State Anxiety (pre-test)[a]	35.8†	9.7	29.5	7.5	32.3	10.7
State Anxiety (post-test)[a]	32.4	8.5	30.7	7.9	32.5	12.0
Dispositional optimism[a]	9.4	3.7	9.8	4.5	11.7	5.6
Expectations AP	.80	1.5	1.28	1.6	.59	1.2
Expectations EP	2.20†	1.6	1.90	2.1	.88	1.8

Warmth threshold (t) in °C[a]	34.0	1.3	33.5	0.6	34.2	1.6
Heat threshold (T) in °C[a]	40.9	3.6	40.2	3.5	41.2	3.3
Temperature low pain in °C[a]	42.9	3.7	44.2	3.0	43.2	3.4
Temperature moderate pain in C[a]	46.1	2.6	46.8	2.2	46.0	2.5
NRS low pain AP[a]	1.7	1.4	1.2	1.0	1.1	0.9
NRS moderate pain AP[a]	4.3	1.4	4.0	1.7	3.4	1.4

[a]Based on one-way ANOVAs. [b]Based on chi-square Test. †Alpha level was set at .05, Bonferroni corrections were applied for multiple comparisons. *AP = acquisition phase, EP = evocation phase.*

Manipulation checks

A significant interaction effect was found for Group x Cue in the acquisition phase ($F(2,85) = 76{,}327$, $p < .001$, $\eta p^2 = .642$). Bonferroni corrected post hoc tests revealed significant mean differences between pain scores after “ON” and “OFF” cues in the OLP group ($M = 2.5$, SD = 0.2, 95% CI = 2.1-2.9; $p < .001$) and the DP group ($M = 2.9$, SD = 0.2, 95% CI = 2.5-3.3; $p < .001$), whereas in the control group no significant differences were found between ‘ON’ and ‘OFF’ cues ($M = 0.2$, $SD = 0.2$, 95% CI = -0.6-0.2; $p = .367$) (see **Figure 2**). A significant main effect of the within-subject factor cue was found (“ON” versus “OFF”; $F(1,85) = 255{,}431$, $p < .001$, $\eta p^2 = .750$) and a significant main effect of the between subjects factor group was found ($F(1,85) = 3{,}115$, $p = .049$, $\eta p^2 = .068$).

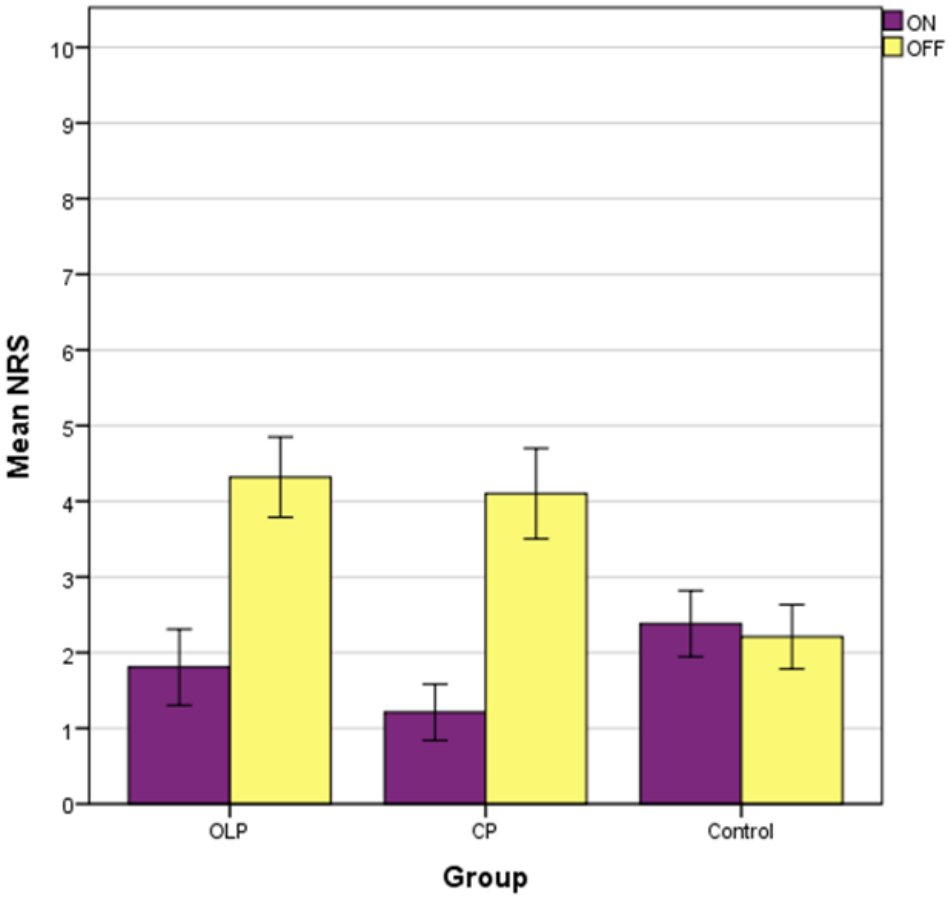


Figure 2. Mean NRS pain scores from the acquisition phase after “ON” and “OFF”. Error bars are depicted with 95% CI. A significant interaction effect of Group X Cue indicated a difference between “ON” and “OFF” for the experimental groups, but not in the control group. *NRS = numeric rating scale.*

To explore the time course of the acquisition phase, all ten “ON” and “OFF” trials were analyzed which revealed a three-way interaction effect of Group x Cue x Time, $F(18,603) = 16.737$, $p < .001$, $\eta p^2 = .333$. Bonferroni corrected post hoc tests were conducted to compare interaction effects of Time x Cue per group and revealed that the effects of conditioning, in which pain ratings congruently differed after “ON” and “OFF” cues over time for the OLP and DP groups, were not present in the control group. To indicate, pairwise comparisons of all ten trials revealed no significant differences across the “ON” cues over time in the OLP group and the DP group, and this same pattern was also observed across all of the ten “OFF” cues. For the control

group however, NRS ratings for “ON” and “OFF” cues differed over time and were different for almost every “ON” and “OFF” cue (see **Figure 3**).

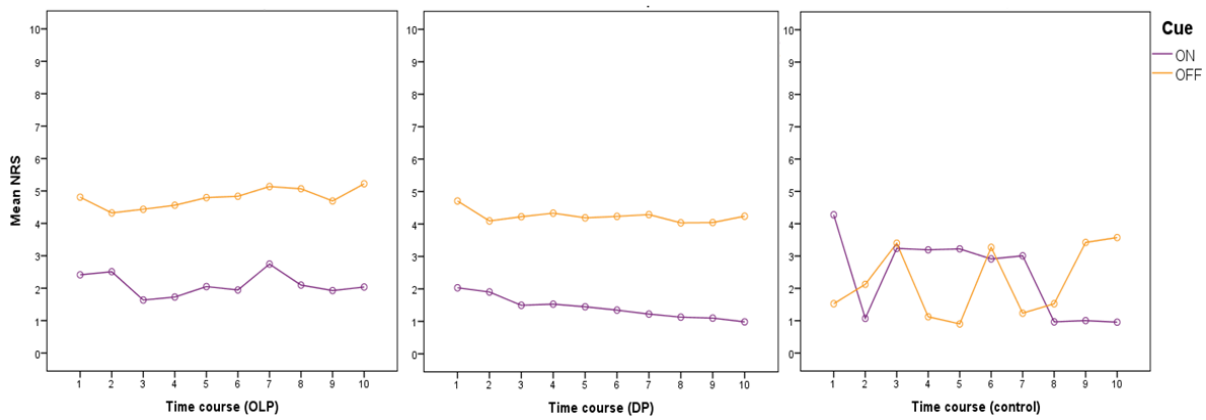


Figure 3. Time course of the pain scores after “ON” and “OFF” trials of the acquisition phase for all three groups.

For the time course of expectations from the acquisition phase, we found a three-way interaction effect of Group x Cue x Time F(2,84) = 9.819, p < .001, ηp2 = .189. Bonferroni corrected post hoc tests revealed that for the first comparison of the expectation questions (based on the first “ON” cue versus the first “OFF” cue), participants reported no differences in expected pain ratings in the OLP group (M = 0.1, SD = 0.3, 95% CI = -0.5-0.7; *p* = .730) and the DP group (M = 0.3, SD = 0.3, 95% CI = -0.3-0.9; *p* = .298). For the second comparison of “ON” versus “OFF” cues, a significant difference was found between expected pain ratings in the OLP group (M = -2.2, SD = 0.4, 95% CI = -3.0, -1.4; *p* <.000) and the DP group (M = -1.6, SD = 0.4, 95% CI = 0.8-2.5; *p* <.000). In the control group, significant differences were found in expectancy ratings before the first comparison of “ON” and “OFF” cues (M = -1.3, SD = 0.3, 95% CI = -1.9,=-0.7; *p* < .000), and also for the second comparison (M = 1.0, SD = 0.4, 95% CI = 0.2-1.8; *p* = .018).

Primary outcome: Evocation phase OLP versus control group

A significant interaction effect was found for Group x Cue, *F*(1,57) = 5.207, *p* = .026, ηp^2 = .084). Planned contrast revealed that the interaction effect was driven by participants from the OLP group, where significant higher mean differences were

found between “ON” and “OFF” trials (*M* = 0.9, *SD* = 0.2, 95% confidence interval (CI) = .5-1.3; *p* <. 001), whereas the control group did not show this difference (*M* = 0.2, SD = 0.2, *p* = .416, 95% CI = -0.3-0.6; *p* = .416). Differences between “ON” and “OFF” cues in the OLP group were mainly caused by higher pain scores after an “OFF” cue, which were significantly higher in the OLP group (*M* = 4.6, *SD* = 0.3, 95% CI = 3.9-5.2), than the control group (*M* = 3.5, *SD* = 0.3, 95% CI = 2.8-4.2; *p* = .027) (see **Figure 4**).

There was a significant main effect of Cue on pain scores indicating that pain scores after the “ON” cue were significantly lower than pain scores after an “OFF” cue (*F*(1,57) = 12,040, *p* = .001, ηp^2 = .174). Furthermore, a marginally significant main effect on the between-subject level was found (*F*(1,57) = 2.960, *p* = .091, ηp^2 = .049), which showed that overall pain scores in the OLP group were marginally higher than pain scores in the control group.

Secondary outcome: OLP versus DP group

No significant interaction-effect of Group x Cue was detected (*F*(1,58) = .116, *p* = .734, ηp^2 = .002). A significant main effect on within-subject level was found for Cue, *F*(1,58) = 22.358, *p* < .001, ηp^2 = .278, revealing that pain scores after an “ON” cue were significantly lower than pain scores after “OFF” cues. A marginally significant effect on the between-subjects level was found (*F*(1,58) = 3.043, *p* = .086, ηp^2 = .050).

To exploratively compare all three groups, an additional mixed ANOVA was conducted with all groups and revealed a marginally significant interaction effect between Group and Cue, *F*(2,85) = 2.509, *p* = .087, ηp^2 = .056) (see **Figure 4)**. Since the specific group comparison contrasts were pre-planned in the Dutch Trial Register (Trial NL8220), we furthermore explored subsequent group difference despite the non-significance interaction. Bonferroni corrected post hoc tests yielded a trend towards significant mean differences between pain scores from the OLP and the control group (*M* = 1.1, *SD* = 0.5, 95% CI = -2.3; *p* = .081), but no significant mean differences were found for OLP versus DP (*M* = 0.8, *SD* = 0.5, 95% CI = = -0.4-2.0; *p* = .291) or DP versus control (*M* = 0.3, *SD* = 0.5, 95% CI = = -0.9-1.5; *p* = 0.999). A significant main effect on the within-subjects level was found between “ON” and “OFF” cues, *F*(1,85) = 20,219, *p* < .001, ηp^2 = .192). No between-subject effect was

found $F(1,85) = 2,112$, $p = .127$, $\eta p^2 = .047$). Because we found higher levels for pre-test STAI in the OLP group, we conducted an additional analysis with pre-test STAI as a covariate, but this did not change the results ($F(1,82) = .295$, $p = .589$). Even though pain expectations from the evocation phase also revealed a significant difference in the OLP group, we did not include this as a covariate, because we assumed this to be the result of our research manipulations (verbal suggestions and placebo rationale).

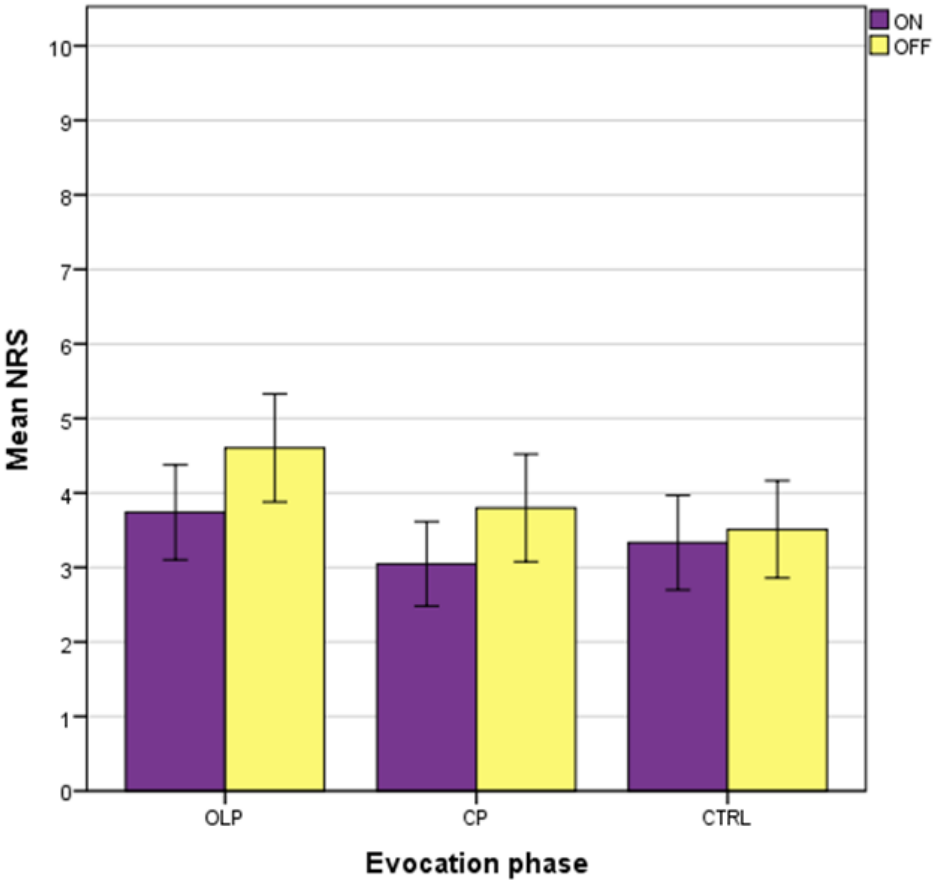


Figure 4. Mean NRS pain scores for the first trials of the evocation phase after "ON" and "OFF" cues for all three groups. Error bars are depicted with 95% CI. A main effect on within-subjects level was found between "ON" and "OFF" cues. *OLP = open-label placebo, DP = deceptive placebo, NRS = numeric rating scale.*

To explore the time course of the evocation phase, pain scores from all separate three "ON" and three "OFF" trials were analyzed, which revealed a non-significant interaction effect of Group x Cue x Time, $F(4,170) = .439$, $p = 780$, $\eta p^2 = .010$). No other significant main or interaction effects were found, except for a

significant within-subject effect of Cue $F(1,170) = 29.617$, $p < .001$, $\eta p^2 = .258$) (see **Figure 5**).

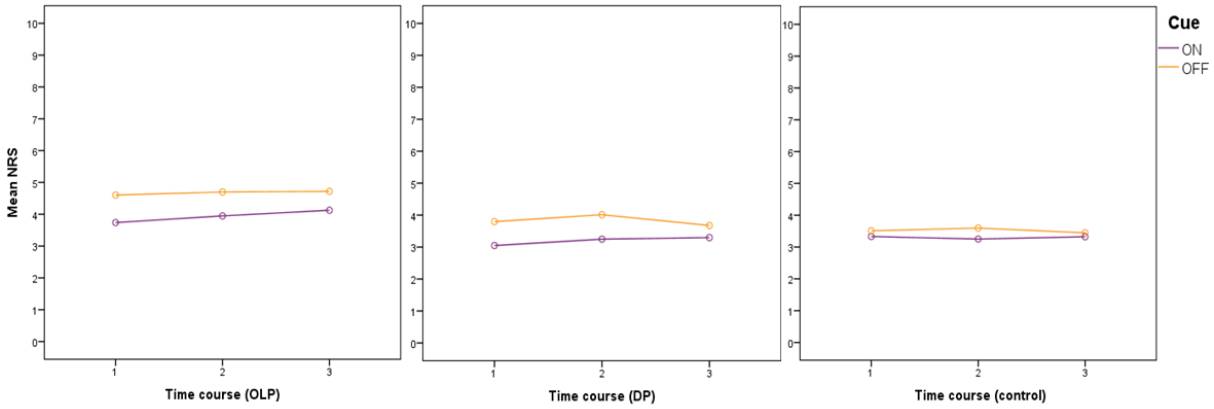


Figure 5. Time course of the pain scores after "ON" and "OFF" trials of the evocation phase for all three groups.

Questionnaires and pain expectations

Pearson correlation analysis revealed a significant relationship between the magnitude of placebo effects with pain expectations from the acquisition phase ($r = -.297$, $p = .021$) and pain expectations from the evocation phase ($r = -0.607$, $p < .001$). No significant associations with the magnitude placebo effects were found for the other outcome variables pre-test state anxiety ($r = 0.08$, $p = .551$), post-test state anxiety ($r = 0.77$, $p = .561$), and dispositional optimism ($r = -.169$, $p = .196$).

Finally, stepwise multiple regression analysis revealed that expectations from the evocation phase were a predictor for the magnitude of placebo effects (b = -.61, t(59) = -5,810, $p < .001$), and explained a significant proportion of the variance in placebo effects, $R^2 = .607$, $F(1,58) = 33.762$, $p < .001$. Expectations from the acquisition phase did not predict the magnitude of placebo effects (b = -0.41, t(2,59) = -.350, $p = .728$, and did not add to the explained variance of the regression model, $R^2 = .608$, $F(1,57) = .123$, $p = .728$.

DISCUSSION

In this study, we investigated the analgesic effects of OLP in a well-validated heat pain conditioning paradigm combined with positive verbal suggestions and newly developed placebo instructions. Our primary research aim was to compare placebo effects (measured as the difference in pain scores between placebo activation and deactivation) of OLPs to a control group that did not undergo a conditioning procedure, nor received positive verbal suggestions. Our results demonstrated significantly larger differences in pain outcomes in the OLP group compared to the control group. Furthermore, in line with our second hypothesis, we found no significant differences in analgesic effects between the OLP and DP group, that differed in the placebo rationale provided in the OLP group. A comparison with all three groups mitigated the placebo effect and revealed a marginally significant difference in pain scores between the groups. Our manipulation check revealed that the sham treatment was successful in eliciting placebo effects when combined with a conditioning procedure, which was signified by lower pain scores after “ON” cues and higher pain scores after “OFF” cues in both placebo groups, and this pattern was not present in the control group that underwent a sham conditioning procedure. Finally, we investigated the role of psychological measures on the magnitude of placebo effects, and found that expectations about forthcoming pain from the evocation phase were a significant predictor for placebo effects.

Compared to previous findings from OLP studies with healthy controls, our study is one of the first to demonstrate an effect of OLPs over a control group on pain scores after placebo induction in an experimental setting(15, 16, 21). So far, studies with OLPs have mostly been carried out with clinical samples, and inducing OLP effects in healthy volunteers faced several challenges. To indicate, a recent study with healthy controls by Kube and colleagues found effects of OLP on pain tolerance, but not on subjective pain reduction(15), and another OLP study by Locher and colleagues found no differences in subjective pain intensity between OLP groups and a control group(21). In contrast, OLP studies with clinical samples have more frequently demonstrated significant effects of OLP compared to control groups and generally report medium to large effect sizes (13, 14, 18). Kube and colleagues explained this discrepancy in findings of OLP effects in healthy controls and patient samples by the desire for pain relief in participants. The desire for pain relief may be

higher for patients with actual pain in clinical samples, than in healthy individuals who received experimentally induced and temporal pain stimulations. Moreover, previous studies with healthy volunteers mainly made use of instructional learning to induce OLP effects whereas the present study combined this with conditioning principles and may have therefore found an OLP effect over a control group. Conversely research with OLPs in experimental settings with healthy controls can be challenging, but is necessary to study the underlying mechanisms of OLP in order to optimize the application of these principles to vulnerable patient samples(15).

In our secondary analysis, we compared the effects of OLPs and deceptive placebos and found no differences in pain relief when participants were made aware of the sham treatment compared to a deceptive state. This finding, again, is a replication of OLP findings in clinical research, whereas experimental studies frequently found deceptive placebo effects to be stronger than OLP effects (7, 13-20). A possible but cautious explanation for this finding (or specifically the lack thereof in the OLP and DP group), may be due to the combination of conditioning principles and instructional learning. Hitherto, only one previous experimental study demonstrated that conditioning principles can be applied and may be relevant to induce OLP effects to a similar extent as DPs; this study used a within-subject design that included a pre and post OLP reveal whereas the current research design used a between-subjects group comparison design. Both studies demonstrated OLP effects when combining conditioning principles with positive expectations (20). Finally, we assessed psychological measures that were selected based on their previous association with placebo effects, namely state anxiety, dispositional optimism and expectations about forthcoming pain. In contrast to previous study findings, we did not find significant associations between placebo effects and state anxiety(6) or dispositional optimism(3). These non-significant findings may be due to the fact that OLPs do not share the same association with psychological measures as (deceptive) placebo effects. For example, findings from a previous study underlined the differential role of dispositional optimism for OLP and DPs(21) and this may also be the case for other psychological measures commonly associated with placebo effects. Furthermore, we found that pain expectations from the evocation phase showed a significant association with the magnitude of placebo effects, whereas this association was not found for pain expectations of the acquisition phase. A reason for these findings may pertain to the fact that expectations form over time, and were

not established in the beginning of the acquisition phase yet[6]. This was also observed in the first comparisons of the expectation questions where no difference was found in expected pain for “ON” and “OFF” cues, but became present after the second comparison from the acquisition phase, and the third comparison from the evocation phase. For this reason, we would suggest in future research to carry out expectation questions more towards the end of the acquisition phase, because participants may have formed more stable expectations by then. These findings underline the importance to stimulate positive expectations for both OLP and DP effects(8, 34, 35). To elucidate more important psychological constructs involved in generating an OLP effect, further research is needed.

Importantly, there are several important considerations that need to be taken into account while interpreting our results. First, this research design is not able to uncover independent effects of the conditioning procedure and instructional learning. Because these mechanisms were combined in the placebo groups, this research design only reveals that combining these mechanisms significantly altered pain outcomes in the placebo groups. However, there are some indications that reveal the effects of conditioning and verbal suggestions alone. For example, with our manipulation check from the conditioning phase we were able to uncover that participants from the placebo groups formed associations between low pain levels and “ON” cues, and moderate pain levels and “OFF” cues, which were not observed in the control group. Another consideration is that we found a trend that indicated higher NRS scores after “OFF” cues in the OLP group compared to the other groups. However, this tendency was presumably formed during the acquisition phase in which NRS scores after “OFF” cues were also somewhat higher than the other groups. Second, in contrast to other studies, in the current study we did not differentiate between colors associated with “ON” and “OFF” cues. In this study, all participants saw a yellow “ON” cue and a purple “OFF” cue, because we selected colors that were disassociated with pain intensities from previous literature(28). . Moreover, we found a significant mean difference for expectations in the OLP group compared to the DP and control group, which might support the efficacy of the placebo rationale, since this information was the only aspect that distinguished the OLP group from the DP group. Whilst the exact content of open-label placebo instructions has not been studied much, we aimed to provide instructions that were

as comprehensive as possible based on the preferences for placebo information strategies from previous placebo research[30]. In future research, we encourage researchers to further examine the content of placebo information used for OLP, possibly in a more personalized manner. Lastly, an important limitation of the present study was the sample that was recruited. Although we aimed to recruit a homogeneous group from 16 to 35 years, we recognize its restrictions to generalizability and encourage future researchers to recruit a more heterogeneous sample.

Altogether, we demonstrated the potential to combine a conditioning paradigm, positive verbal suggestions and a placebo rationale to induce analgesic effects with OLPs. Our findings are in line with previous research that uses a conditioning paradigm to induce placebo effects, namely that NRS scores are higher after placebo deactivation and lower NRS scores after placebo activation. In the control group these differences were not present, because only half of the activation cues were followed by low pain intensity, and half of the deactivation cues were followed by moderate pain intensities, thereby preventing the effects of conditioning to occur. To further disentangle the underlying mechanisms of OLPs, further research is warranted in different experimental contexts to explore the potential for clinical application.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary file 1: Leaflets of placebo information for all groups

S 1: Leaflets of placebo information for all groups
Leaflet for Open-label placebo group (1/2)

Electrical nerve stimulation (ENS) can decrease pain

What is ENS?

Electrical Nerve Stimulation (ENS) is the administration of an electric current produced by a special device that can affect nerve fibres. ENS decreases nerve conduction.

Scientific research found support for the effectiveness of ENS for chronic numbness of the lower limbs, lateral epicondylitis (tennis elbow), and carpal tunnel syndrome (Chesterton et al., 2016; Koca, Boyaci, Tutoglu, Ucar, & Kocaturk, 2017; Mulvey, Fawkner, Radford, & Johnson, 2016).

How does ENS affect pain?

Heat pain is decreased by ENS through nerve fibre conductivity. Indeed, nerve fibres in the skin communicate what is perceived via electrical signals. When these signals are sent to the spinal cord and brain, we become aware of the pain sensations. ENS stimulation can influence this conductivity process by decreasing the intensity of incoming signals. This means that pain caused by stimuli applied on the skin, such as heat stimuli, can be decreased by this device (Chen & Johnson, 2017; Schliessbach, Klift, Arendt-nielsen, Curatolo, & Streitberger, 2016).

ENS decreases pain

ENS treatment has repeatedly been found to decrease pain from heat, as a side effect of decreased nerve conduction (Vance, Dailey, Rakel, & Sluka, 2017). A recent study showed that 92% of the participants reported substantially lower pain when they received heat stimuli during ENS (Ellrich & Lamp, 2017).

Sub perception stimulation

Some studies shown that slight electrical pulses, below the perception level, can modulate deep electrical signal conduction (Chen & Johnson, 2017, 2018). So clinically, a big advantage of ENS is that an (almost) imperceptible stimulation is sufficient to affect electrical conduction and thus reduce the perceived pain (Ellrich & Lamp, 2017).

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PAIN PERCEPTION AND PLACEBO EFFECTS

The Placebo Effect

Now, some more information follows about the purpose of this study. This study focuses on placebo effects. Placebo effects are a common phenomenon in scientific research and clinical practice.

In treatment studies, overall treatment effects are the result of two mechanisms:

- The treatment effect itself (red bar in figure);
- The placebo effect (blue bars in figure) which is dependent on factors such as previous experience, expectations and the physician-patient interaction.

As you can see in the picture, the placebo effect has a large influence in the total treatment effect. Placebo effects can thus **increase** therapeutic effects.

How do placebos work?

- **Expectations** have a big impact on treatment outcomes. If you have **positive expectations**, they may develop a more positive treatment outcome and affect your pain experience in this present study. You may not only feel better from the procedure itself, but also because you expect to feel better.
- Positive expectations also affect **processes** in your body**.** When you have positive expectations, the brain produces chemicals. These chemical substances are called **neurotransmitters** and can make you feel better. Placebos can also trigger the release of neurotransmitters. In this study we will be making use of these processes to reduce pain.

In this study we want to induce placebo effects with the ENS device. The device will be switched off during the experiment, but it is definitely possible that you experience less pain because of placebo effects.

S 1: Leaflets of placebo information for all groups

Leaflet for Deceptive placebo group (1/1)

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S I: Leaflets of placebo information for all groups

Leaflet for the control group (1/1)

Electrical nerve stimulation (ENS)

What is ENS?

Electrical Nerve Stimulation (ENS) is the administration of an electric current produced by a special device that can affect nerve fibers.

Can ENS affect pain?

Nerve fibers in the skin communicate what is perceived via electrical signals. When these signals are sent to the spinal cord and brain, we become aware of the pain sensations. Because ENS induces stimulations, this may have an effect on the intensity of incoming pain signals. Few studies have examined this. Some patients have reported to benefit from the effects of ENS, but other patients report that it doesn't make any difference in their experience of pain. With this study, we will investigate whether there is support or not for this conductivity theory.

Sub perception stimulation

Some studies show that slight electrical pulses, below the perception level, can modulate deep electrical signal conduction. This study will measure (almost) imperceptible stimulations.