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Psychological Placebo and Nocebo Effects on Pain Rely on Expectation and Previous Experience

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Abstract: Expectation and previous experience are both well established key mediators of placebo and nocebo effects. However, the investigation of their respective contribution to placebo and nocebo responses is rather difficult because most placebo and nocebo manipulations are contaminated by pre-existing treatment expectancies resulting from a learning history of previous medical interventions. To circumvent any resemblance to classical treatments, a purely psychological placebo-nocebo manipulation was established, namely, the "visual stripe pattern–induced modulation of pain." To this end, experience and expectation regarding the effects of different visual cues (stripe patterns) on pain were varied across 3 different groups, with either only placebo instruction (expectation), placebo conditioning (experience), or both (expectation + experience) applied. Only the combined manipulation (expectation + experience) revealed significant behavioral and physiological placebo–nocebo effects on pain. Two subsequent experiments, which, in addition to placebo and nocebo cues, included a neutral control condition further showed that especially nocebo responses were more easily induced by this psychological placebo and nocebo manipulation. The results emphasize the great effect of psychological processes on placebo and nocebo effects. Particularly, nocebo effects should be addressed more thoroughly and carefully considered in clinical practice to prevent the accidental induction of side effects.

***Perspective:** Even purely psychological interventions that lack any resemblance to classical pain treatments might alter subjective and physiological pain correlates. A manipulation of treatment expectation and actual treatment experience were mandatory to elicit this effect. Nocebo effects were especially induced, which indicated the necessity for prevention of accidental side effects besides exploitation of placebo responses.*

***Key words:** Psychological placebo intervention, placebo hypoalgesia, nocebo hyperalgesia, experience, expectation.*

Placebo and nocebo effects represent ideal examples for the tremendous effect of psychological processes on pain.[4,5,40] They have been shown to result in alterations of biological pain markers[19,41] and to be distinct from other psychological pain modulatory mechanisms such as distraction.[9] Expectation and previous experience are key mediators of placebo hypo- or nocebo hyperalgesia[36] and their effects and interactions have been shown in a variety of experimental paradigms.[4,12,32] In 2 seminal studies, the influence of previous learning for the generation of a subsequent placebo effect was shown: After a placebo conditioning procedure (placebo cream paired with low levels of pain, control cream paired with higher levels of pain) participants showed placebo analgesia in a subsequent test phase when pain stimuli were actually of identical physical intensity.[38,39] Since then, it has been shown that even social observational learning is capable of eliciting placebo[11] and nocebo[37] effects, and also manipulations of expectations by suggestion or verbal instruction were found to induce placebo effects.[1,14] In general, the strongest placebo and nocebo

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effects were observed when expectation and experience were manipulated in concert.[10,12,39] However, it remains to be shown whether the 2 mechanisms act independently from each other in a mainly additive manner or if they result in an interactive (ie, over or under additive) modulation of pain.[9,16]

With regard to medical practice, the repeated encounter of an intervention in association with a specific stimulus or context (eg, capsule, white coats, the hospital itself) leads to the generation of cues that predict the actual drug or treatment effect, and thus shape future treatment expectations. As a result, these cues might elicit conditioned (placebo and nocebo) reactions themselves, such as symptom decrease or increase.[16,40] It was shown that previous experiences with an intervention modulate the placebo response and further that placebo effects are embedded in an individual's history of medical treatments.[15,23]

So far, placebo and nocebo paradigms of pain were conducted usually with application of placebo agents that provided pharmacological plausibility or resembled medical interventions, for example, inert creams,[18] prickling nasal sprays,[33] injections,[42] sham acupuncture,[26] fake low-current electrical stimulation,[13] etc. Consequently, investigation of the contribution of experience and expectation to placebo and nocebo effects separately is rather difficult, because the usage of medical sham treatments might always activate expectations that are the result of individual treatment experiences.[17] We concluded that experimentally induced placebo or nocebo effects are likely contaminated by expectations as a result of the individual's history of previous treatments. Therefore, the present study was designed to manipulate experience and expectation independently and to forego any resemblance to popular pain treatments by taking advantage of a purely psychological placebo–nocebo paradigm. To this end, in experiment 1 we compared 3 groups of participants. One group received a written placebo–nocebo instruction, which provided information about the alleged powerful analgesic and proalgesic effects of watching certain black and white stripe patterns (expectation). The second group (experience) underwent placebo–nocebo conditioning with these stripe patterns as visual cues, and the third group received the placebo–nocebo instruction and the conditioning procedure (expectation + experience). In a subsequent test phase, placebo and nocebo responses were measured by applying identical thermal pain stimuli. In experiments 2a and b, an additional neutral control stimulus was introduced to determine whether the manipulation resulted primarily in a placebo or a nocebo effect. In contrast to previous studies, which used predictive cues that solely announced different upcoming pain intensities,[2,31] in the present experiments participants were informed about an actual pain modulatory effect that would result from observation of the described visual stripe patterns.

Our main goal was to test whether a purely psychological placebo–nocebo manipulation would be feasible to induce placebo hypo- and nocebo hyperalgesia. Furthermore, we aimed to elaborate whether 1) expectation and experience would modulate pain independently from each other (additive contribution), 2) a combination of expectation and experience would lead to mutual interference and thus decreased responses (underadditive interaction), or 3) the manipulation of expectation and experience would result in a disproportionally pronounced placebo–nocebo response (overadditive interaction).

Methods

Participants

In experiment 1, 65 participants (32 women, mean [M] = 23.62 years, SD = 3.18) were randomly allocated to 1 of the 3 experimental groups. Participants of the different groups did not statistically differ from each other regarding their individual pain threshold (PT; P = .99), pain sensitivity (P = .99),[34] or trait anxiety (P = .22).[35] Participants of the expectation group were slightly younger (M = 21.86 years, SD = 2.96) than participants of the experience group (M = 24.65 years, SD = 3.45) and the combined expectation + experience group (M = 24.39 years, SD = 2.44), $F_{1,64} = 5.87$, P = .01.

In experiment 2a, 29 participants took part; of those, 3 participants were excluded because of technical problems with pain stimulation or insufficient understanding of the experimental procedure, which resulted in a final sample of 26 participants (14 women, age M = 25.27 years, SD = 6.33).

In experiment 2b, 23 participants took part; of those, 3 participants were excluded because of exceedingly high PTs, which resulted in a final group size of 20 (14 women, age M = 23.20 years, SD = 2.78).

All participants of experiments 1 and 2a and b had no current, or history of, chronic pain, neurological or psychiatric disorder, and did not take any pain medication 24 hours before the experiment (self-report). Informed consent was obtained from all participants before participation in the study. The experimental procedure was approved by the institutional review board of the medical faculty of the University of Würzburg.

Thermal Pain Stimulation

Pain stimuli were delivered using a Somedic MSA thermal stimulator (Somedic Sales AB, Hörby, Sweden) and a Peltier thermode with an active surface of 25 × 50 mm. Before the actual experiment, the individual PT was assessed. The average PT temperature in experiment 1 was M = 46.56°C, SD = 2.34°C (groups did not differ, F < 1), and M = 45.51°C, SD = 2.88°C in experiment 2a. Thermal stimulation started from a baseline temperature defined as 10°C lower than PT and increased with a speed of 5°C/s until low pain (PT), medium pain (PT + 0.5°C), or high pain (PT + 1C°) was achieved, respectively.

In experiment 2b, placebo, control, and nocebo temperatures were generated on the basis of a calibration procedure (similar to the procedure described previously[19]) during which the participants evaluated the pain intensity of 10 heat pain stimuli (range

43.5–48.0°C) on a visual analogue scale (VAS, scale of 0–100). Pain ratings were fitted with a linear regression and stimulation levels were chosen, which approximated VAS 40, 50, and 60 (45.14°C, 46.16°C, and 47.18°C, respectively). This procedure was applied to guarantee 3 distinct temperature levels during conditioning despite individual differences in pain perception.

All participants rated the pain stimuli regarding pain intensity and pain unpleasantness using a digitized VAS ranging from 0 = "no pain" at all to 100 = "unbearable pain" (pain intensity), and from 0 = "not unpleasant at all" to 100 = "extremely unpleasant" (pain unpleasantness) using a button press of a computer keyboard.

Skin Conductance Measurement

For skin conductance recording, two 22/10 mm Ag/AgCl surface electrodes (electrode gel: 0.5% NaCl) were attached to the thenar and hypothenar eminence of the participant's nondominant hand. The signal was sampled with 1000 Hz, with constant application of 0.5 V, using a V-Amp amplifier (Brain Products Inc, Munich, Germany) and recording software (Brain Vision Recorder, V. 1.10, Brain Products Inc). Skin conductance responses (SCRs) were quantified as highest positive deflection 1 to 13 seconds after pain stimulation onset, relative to a 1-second baseline (Brain Vision Analyzer 2.0., Brain Products Inc). Two participants of experiment 1 (1 of the expectation group; 1 of the combined expectation + experience group) showed no responses during the whole test phase and were excluded from the SCR data analysis.

Placebo–Nocebo Manipulation and Experimental Procedure

Experiment 1

Participants were instructed according to their experimental group either to take part in a study on the processing of thermal pain (experience), or that they were going to watch horizontal and vertical black and white stripe patterns, which reportedly had been shown in studies by renowned scientists to drastically decrease or increase the perception of pain (expectation, expectation + experience). Participants then were familiarized with the pain stimulation and rating procedure, and proceeded to the conditioning phase consisting of 30 trials (15 placebo cues and low pain; 15 nocebo cues and high pain), followed by the test phase consisting of 20 trials (10 placebo cues and high pain; 10 nocebo cues and high pain). During each trial, the respective visual placebo or nocebo cue was presented in the center of the screen for 20 seconds. Three seconds after cue onset the pain stimulation was started, reached the target temperature after approximately 2 seconds, and remained at plateau for 3 seconds. After the thermode had cooled to baseline level, participants rated their pain experience. Each trial was separated by an intertrial interval of 4 to 5 seconds (randomized) during which a central fixation cross was presented. During the conditioning phase, the expectation group received in random order the same number of high pain and low pain stimulations as the other groups, while watching a central fixation cross. In the subsequent test phase all participants watched placebo and nocebo cues again and received always the identical high pain stimuli (Fig 1). At the end of the experiment, nocebo and placebo cues were presented again and participants were asked to indicate how painful they remember the pain stimulation after the respective visual cue (recalled pain ratings). Recalled pain ratings of the experience and the expectation + experience groups likely reflected the test phase and the conditioning phase when pain stimulation actually was different during the placebo and nocebo trials and therefore need to be interpreted cautiously. Ratings of the expectation group instead referred to the instruction in the beginning of the experiment and probably reflect the manipulation of expectancy because participants never received any contingent pairing of pain stimulation and placebo or nocebo during conditioning.

Experiment 2a

Participants received a similar manipulation as the combined expectation + experience group except for the introduction of a third cue (gray square) that served as a control condition and was explained to the participants to have no influence on the perception of pain at all. After participants read the placebo and nocebo instructions, they were presented with the visual placebo and nocebo cues and evaluated their expectation regarding a pain increase versus a decrease in effect of the 3 visual stimuli using a 9-point Likert scale that ranged from pain very much decreased (−4) to pain very much increased (+4). Placebo conditioning similarly consisted of the presentation of the placebo cue paired with low pain, the nocebo cue paired with high pain, and the neutral cue paired with medium pain (10 trials per condition). During the subsequent test phase, cues were presented always combined with high pain (10 trials per condition; Fig 1).

Experiment 2b

The paradigm was the same as in experiment 2a, with the exception that placebo, control, and nocebo temperatures were approximated to the subjective VAS ratings corresponding to 40, 50, and 60, respectively. Conditioning consisted of 15 trials per condition as in experiment 1. During the test phase, pain stimuli were always equivalent to the pain stimulation level of the control trials during conditioning (10 trials per condition; Fig 1).

Statistical Analysis

For experiment 1, pain-evoked SCRs, sensory, and affective pain ratings of the test phase were analyzed by applying a 3-factorial repeated measures analysis of variance (ANOVA) with the within-subjects factor condition (placebo vs nocebo), the within-subjects factor time (trials 1-5 vs trials 6-10), and the between-subjects factor experimental group

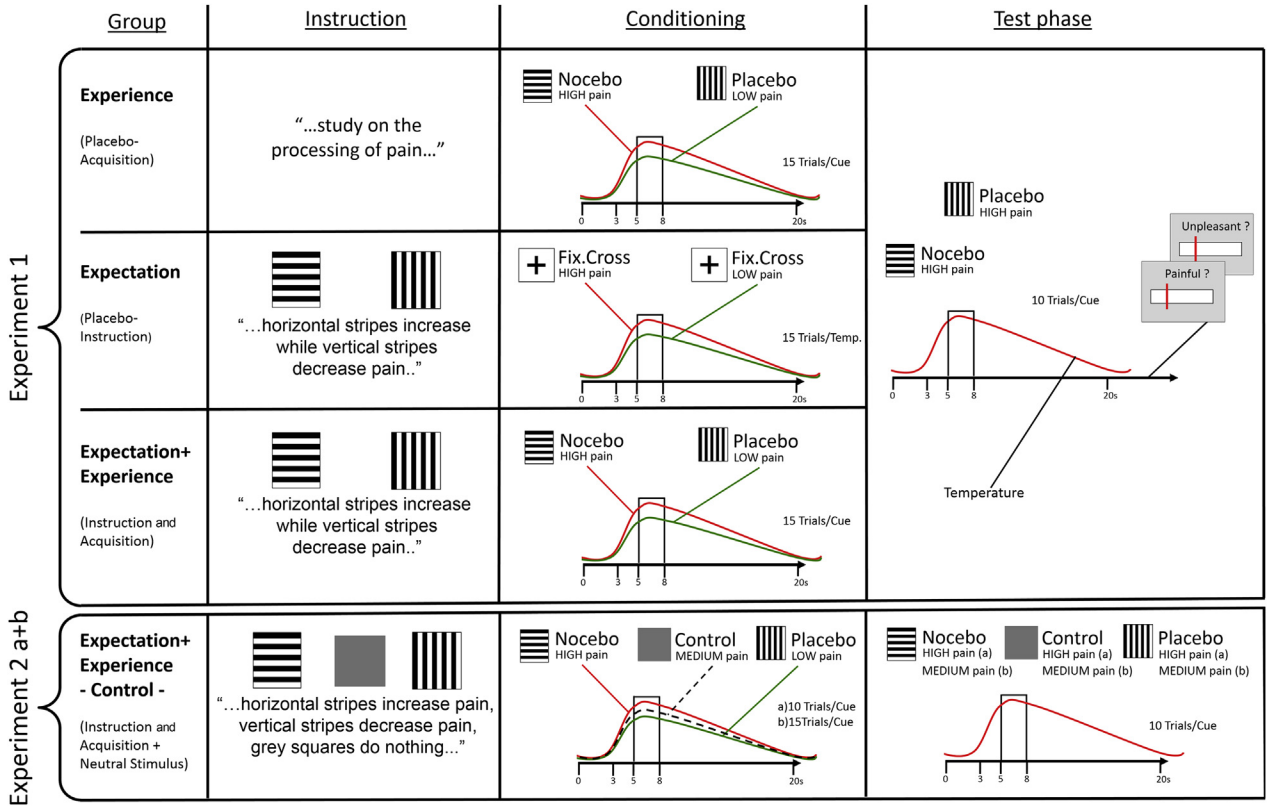

Figure 1. Procedure of experiments 1 and 2. In experiment 1 participants were first instructed according to the respective experimental condition: experience (control instruction: "You are going to take part in a study on heat pain perception") versus expectation, or expectation and experience (placebo–nocebo instruction: "You are going to watch black and white stripe patterns which were found to alter the perception of pain"). Afterwards, participants underwent placebo–nocebo conditioning (experience and expectation + experience group) and watched visual stripe patterns paired with the nocebo or placebo temperature, or watched fixation crosses (Fix.Cross) instead while the same number of pain stimuli were administered (expectation group). At the end of the experiment, participants provided recalled sensory and affective pain ratings for nocebo and placebo cues, respectively. In experiment 2a, only the expectation + experience condition was realized. In addition, a third control stimulus was introduced (gray square), which was stated to have no influence on pain, and was paired with intermediate pain stimulations during conditioning. In the test phase of both experiments, placebo, nocebo, or control cues were paired with a pain stimulus equivalent to the nocebo pain stimuli from the conditioning phase. Experiment 2b was equivalent to experiment 2a, except for the number of conditioning trials (15). Further, temperature levels were calibrated to VAS 40, 50, and 60; the temperature during the test phase was the same as in control trials during conditioning. PT = pain threshold; LOW = PT temperature (experiments 1 and 2a) or VAS 40 (experiment 2b); MEDIUM = PT plus 0.5°C (experiments 1 and 2a) or VAS 50 (experiment 2b), HIGH = PT plus 1.0°C (experiments 1 and 2a) or VAS 60 (experiment 2b).

(expectation + experience vs expectation vs experience). As a manipulation check, results of the conditioning phase were analyzed by applying 2-factorial repeated measures ANOVAs with the within-subjects factor pain stimulation level (low vs high pain) and the aforementioned between-subjects factor group. Similarly, recalled pain ratings at the end of the experiment were analyzed by applying a 2-factorial repeated measures ANOVA with the within-subjects factor placebo versus nocebo and pain stimulation level (low vs high pain) and the between-subjects factor group.

For experiment 2a and b, sensory and affective pain ratings of the test phase were analyzed by applying 2-factorial repeated measures ANOVAs with the within-subjects factor condition (nocebo vs control vs placebo) and the within-subjects factor time (trials 1-5 vs trials 6-10). Similar to experiment 1, results of the conditioning phase were analyzed by applying a repeated measures ANOVA with the within-subjects factor pain stimulation level (low vs medium vs high pain). Associations of pain ratings during conditioning and the subsequent test phase were investigated with linear correlation analysis of nocebo > placebo, control > placebo and nocebo > control difference scores respectively, for sensory and affective pain ratings, separately for each experimental group. When necessary, Greenhouse–Geisser corrections of degrees of freedom were applied. Post hoc comparisons were realized using planned contrasts or pairwise t-tests. A priori significance level was set at $P < .05$, 2-tailed. Partial η^2 (η_p^2) is reported as a measure of effect size.

Results

Experiment 1

The results of the conditioning phase revealed a successful differentiation between the different thermal pain stimulation levels, for sensory pain ratings, $F_{1,62} = 235.54$, $P < .001$, $\eta_p^2 = .79$, and affective pain ratings, $F_{1,62} = 152.87$, $P < .001$, $\eta_p^2 = .71$, Fig 2A). Similarly,

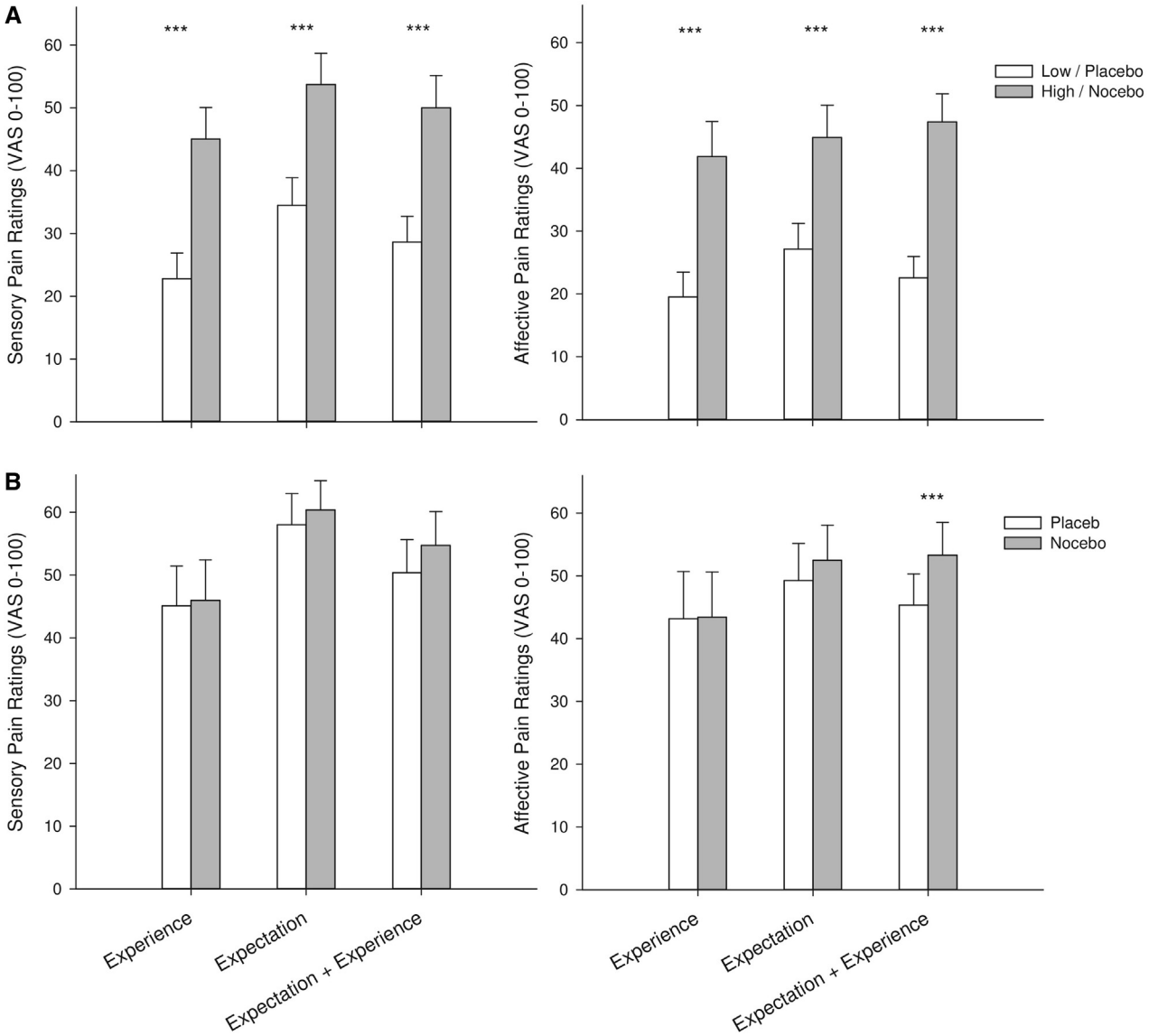

Figure 2. Experiment 1: Mean (±SEM) of sensory and affective pain ratings are depicted for each experimental group. In the conditioning phase **(A)** pain ratings were higher for high compared with low painful stimuli in all experimental groups. In the test phase **(B)** affective pain ratings were higher for nocebo compared with placebo trials only for the expectation + experience group. ***$P < .001$. Abbreviation: SEM, standard error of the mean.

skin conductance responses were higher in response to high compared with low thermal stimulation, $F_{1,62} = 16.37$, $P < .001$, $\eta_p^2 = .21$. In this phase of the experiment, no differences were observed between the 3 experimental groups.

In the subsequent test phase, visual placebo and nocebo cues were presented again, but this time thermal pain stimuli were identical. Placebo and nocebo effects were revealed as follows: The analysis of SCR in response to the thermal pain stimuli indicated a significant 3-way interaction of condition (placebo vs nocebo), time (trials 1-5 vs trials 6-10), and group (expectation, experience, expectation + experience), with $F_{2,60} = 3.16$, $P = .05$, and $\eta_p^2 = .10$, as a result of higher SCR during early nocebo compared with placebo trials (trials 1-5) in the expectation + experience group only, with $t_{21} = 2.90$, and $P = .009$ (Fig 3).

Affective pain ratings revealed a significant effect of condition, with $F_{1,62} = 12.37$, $P < .001$, and $\eta_p^2 = .17$, because of higher unpleasantness ratings for nocebo compared with placebo trials. This effect was further qualified by a significant interaction of condition and experimental group, with $F_{2,62} = 4.28$, $P = .02$, and $\eta_p^2 = .12$. Separate ANOVAs for each group revealed a significant effect of condition for the combined expectation + experience group, with $F_{1,22} = 16.47$, $P < .001$, and $\eta_p^2 = .43$. Instead, this effect was neither significant for the experience ($P = .88$), nor the expectation group ($P = .11$, Fig 2B). There was no effect of time ($F_{1,62} = 0.49$, $P = .83$, $\eta_p^2 = .001$), or a significant interaction of time and condition for affective pain ratings ($F_{1,62} = 0.11$, $P = .74$, $\eta_p^2 = .01$).

Corroborating these findings, post hoc analysis of nocebo minus placebo difference scores in affective pain

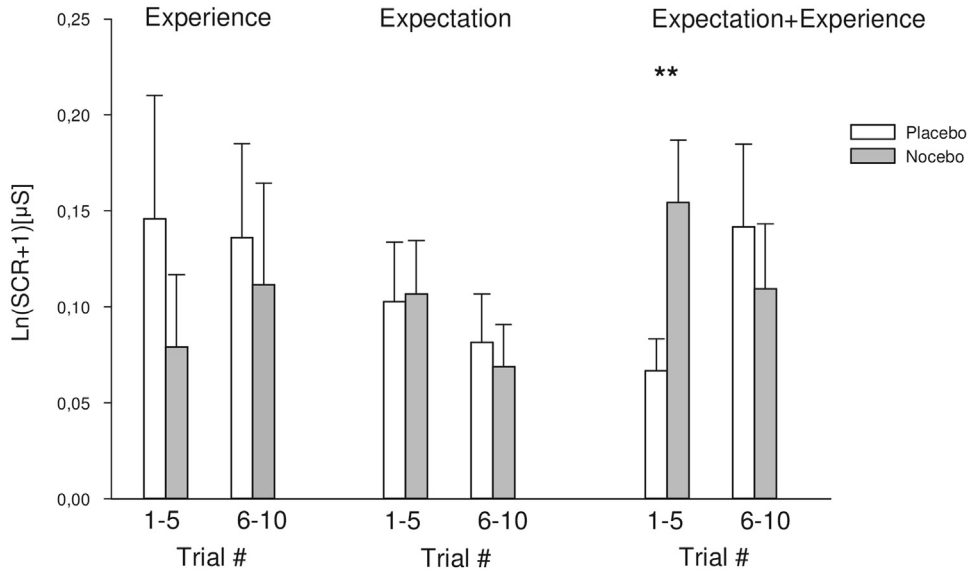

Figure 3. Experiment 1 test phase: SCR (mean ± SEM) in response to the thermal pain stimuli are depicted for each experimental group, split by the first and second half of the test phase. SCRs were increased in the beginning of the test phase for nocebo compared with placebo trials only for the expectation + experience group. $^{**}P < .01$. Abbreviation: SEM, standard error of the mean.

ratings revealed a significantly greater differentiation for the combined expectation + experience group compared with the experience group (t_{62} = 2.88, P = .005), and a marginally significantly greater differentiation compared with the expectation group (t_{62} = 1.81, P = .08, Fig 4). No differences emerged between the expectation and the experience groups (t_{62} = 1.11, P = .27).

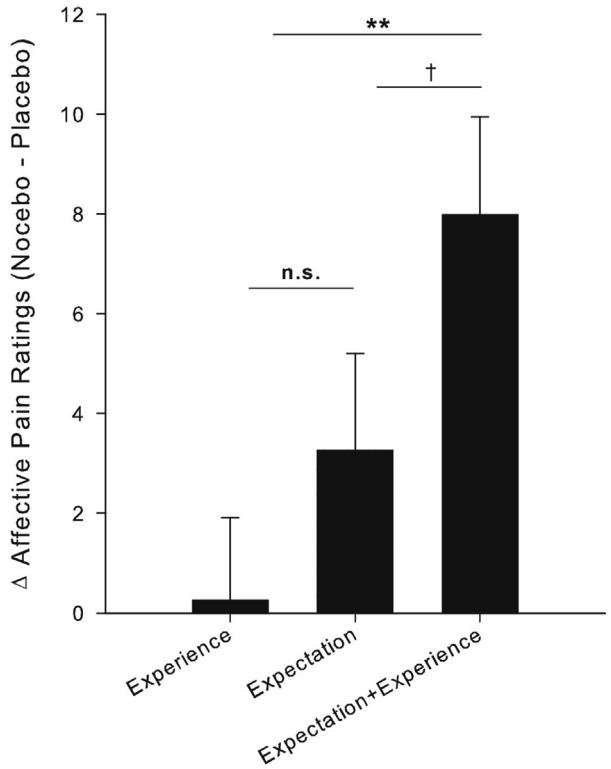

Figure 4. Experiment 1: Depicted are nocebo minus placebo difference scores across all 3 experimental groups (mean ± SEM). The expectation + experience group showed the strongest differentiation of placebo and nocebo trials, followed by the expectation and experience groups. $P > .10$ (not significant [n.s.]); †$P < .10$; $^{**}P < .01$. Abbreviation: SEM, standard error of the mean.

Sensory pain ratings of the test phase were higher for nocebo compared with placebo trials ($F_{1,62}$ = 9.38, P = .003, η_p^2 = .13), irrespective of experimental group or time interval of the test phase. There was no general difference in sensory pain ratings across the experimental groups ($F_{2,62}$ = 1.51, P = .23, η_p^2 = .05). Exploratory comparisons of nocebo and placebo trials revealed a similar picture as for the affective pain ratings, that is, a significant difference for the combined expectation + experience group (t_{22} = 3.40, P = .003), whereas the same comparison was only marginally significant for the expectation group (t_{22} = 1.96, P = .064) and not significant for the experience group (t_{19} = 0.49, P = .63, Fig 2B).

Recalled affective pain ratings at the end of the experiment were higher for nocebo compared with placebo trials ($F_{1,62}$ = 22.38, $P < .001$, η_p^2 = .27) across all groups. Recalled sensory pain ratings were higher for nocebo compared with placebo trials as well ($F_{1,62}$ = 22.35, $P < .001$, η_p^2 = .27). Interactions of condition and group were not significant (P = .11, P = .09, Table 1).

Table 1. Experiment 1: Recalled Sensory and Affective Pain Ratings

Experimental Group	Δ Nocebo-Placebo Pain Ratings	M	SD
Experience (n = 20)	Sensory	12.65	27.01
	Affective	8.60	26.91
Expectation (n = 22)	Sensory	5.10	16.36
	Affective	9.95	20.23
Expectation + experience (n = 23)	Sensory	19.17	18.74
	Affective	21.87	21.56

NOTE. Nocebo > placebo difference scores of recalled sensory and affective pain ratings are shown for each group.

Correlation analysis of nocebo minus placebo difference scores between the conditioning and the test phase revealed a significant linear trend solely for the combined expectation + experience group (affective pain ratings: r = .54, P = .01; sensory pain ratings, r = .50, P = .01), which indicated a relation of reinforced expectations and subsequent recall of the placebo–nocebo response. In contrast, no significant correlations in the 2 other groups were observed (experience: affective pain ratings, r = −.23, P = .32 and sensory pain ratings, r = .17, P = .47; expectation: affective pain ratings, r = −.27, P = .23 and sensory pain ratings, r = −.21, P = .35).

In conclusion, these results from experiment 1 showed significant placebo and nocebo responses and also indicated that their magnitude was predicted by the difference between high and low pain ratings during the learning phase, but only in the group for which instruction and conditioning were combined.

Experiments 2a and b

Experiments 2a and b were designed to follow-up the results of experiment 1 and to determine whether the observed effects were driven more by a placebo or a nocebo response. In experiment 2a, a priori expectancy ratings varied significantly across the different condition cues ($F_{2,50}$ = 15.44, P < .001, η_p^2 = .38). Participants expected the nocebo stripe pattern to result in more pain compared with the control pattern ($F_{1,25}$ = 13.16, P = .001, η_p^2 = .35) and with the placebo pattern ($F_{1,25}$ = 16.91, P < .001, η_p^2 = .40), which they expected to lead to less pain than the control pattern (gray square) ($F_{1,25}$ = 13.15, P = .001, η_p^2 = .30, Fig 5).

In the conditioning phase of experiment 2a, affective pain ratings varied across the 3 pain stimulation levels ($F_{2,50}$ = 43.00, P < .001, η_p^2 = .63). Participants successfully differentiated between high and medium ($F_{1,25}$ = 27.31,

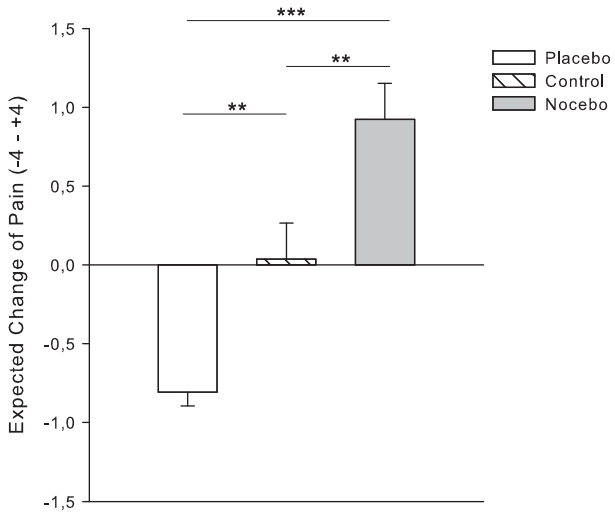

Figure 5. Experiment 2a: Expectancy ratings (mean ± SEM) obtained in the beginning of the experiment; participants expected less pain during placebo and more pain during nocebo trials compared with neutral control trials. **P < .01; ***P < .001. Abbreviation: SEM, standard error of the mean.

P < .001, η_p^2 = .52), high and low ($F_{1,25}$ = 60.42, P < .001, η_p^2 = .71), and also between low and medium pain stimuli ($F_{1,25}$ = 13.19, P = .001, η_p^2 = .35). Similarly, sensory pain ratings varied across the pain stimulation levels ($F_{2,50}$ = 50.12, P < .001, η_p^2 = .67). Participants successfully differentiated between high and medium ($F_{1,25}$ = 44.37, P < .001, η_p^2 = .64), high and low ($F_{1,25}$ = 79.93, P < .001, η_p^2 = .76), and also between low and medium pain stimuli ($F_{1,25}$ = 13.19, P = .001, η_p^2 = .35, Fig 6A). Likewise, pain-related SCRs were modulated by the different pain stimuli ($F_{2,50}$ = 17.31, P < .001, η_p^2 = .41). SCRs were increased for high compared with low ($F_{2,50}$ = 27.40, P < .001, η_p^2 = .52) and medium ($F_{2,50}$ = 17.92, P < .001, η_p^2 = .42) thermal pain stimulation. Medium and low pain stimuli were not significantly different from each other ($F_{2,50}$ = 0.27, P = .61, η_p^2 = .01).

In the test phase, affective pain ratings varied across the 3 different conditions ($F_{2,50}$ = 4.21, P = .02, η_p^2 = .14). Pain stimuli in nocebo trials were rated more unpleasant than in placebo trials ($F_{1,25}$ = 7.04, P = .01, η_p^2 = .22), but only slightly more unpleasant compared with pain stimuli in control trials ($F_{1,25}$ = 3.41, P = .08, η_p^2 = .12). Pain stimuli in placebo trials were rated similar to pain stimuli in control trials ($F_{1,25}$ = 0.93, P = .35, η_p^2 = .04, Fig 6B). The comparison of nocebo > control and control > placebo difference scores was not significant (t_{25} = 0.65, P = .52). No effect of time or an interaction of time and condition were detected. Analysis of pain intensity revealed similar but more pronounced effects. Sensory pain ratings also varied across the 3 different conditions ($F_{2,50}$ = 7.61, P = .001, η_p^2 = .23, Fig 6B). Pain stimuli in nocebo trials were rated as more painful than in placebo trials ($F_{1,25}$ = 13.44, P = .001, η_p^2 = .35), and in control trials ($F_{1,25}$ = 5.32, P = .03, η_p^2 = .18). Pain stimuli in placebo trials were rated only nonsignificantly lower than in control trials ($F_{1,25}$ = 2.56, P = .12, η_p^2 = .09). The comparison of nocebo > control and control > placebo difference scores was not significant (t_{25} = 0.76, P = .45). No effect of time or an interaction of time and condition was detected. Pain-related SCR showed no modulation according to the different conditions during the test phase. Affective pain ratings for placebo > control trials of the conditioning and the test phase were positively correlated (r = .49, P = .01). In addition, sensory pain ratings for nocebo > control trials of the conditioning and the test phase were slightly correlated (r = .35, P = .08). All other correlations failed to reach significance.

In the conditioning phase of experiment 2b, affective pain ratings also varied across the 3 pain stimulation levels ($F_{2,38}$ = 54.23, P < .001, η_p^2 = .74). Participants differentiated between high and medium ($F_{1,19}$ = 49.33, P < .001, η_p^2 = .72), high and low (F (1,19) = 64.42, P < .001, η_p^2 = .77), and between low and medium pain stimuli ($F_{1,19}$ = 22.33, P = .001, η_p^2 = .54). Sensory pain ratings also varied across the different pain stimulation levels ($F_{2,38}$ = 60.37, P < .001, η_p^2 = .76). Participants successfully differentiated between high and medium ($F_{1,19}$ = 60.00, P < .001, η_p^2 = .76), high and low ($F_{1,19}$ = 68.37, P < .001, η_p^2 = .78), and between low and

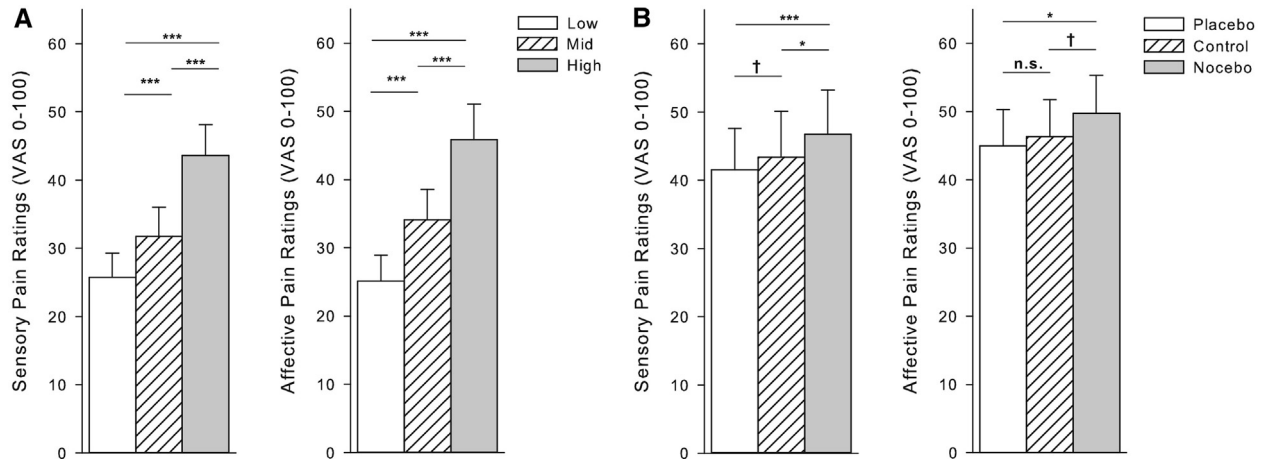

Figure 6. Experiment 2a: Mean (±SEM) of sensory and affective pain ratings are depicted for each experimental condition. In the conditioning phase **(A)** pain ratings significantly differentiated between low, medium, and high pain stimuli. In the test phase **(B)** sensory and affective pain ratings for nocebo trials were rated higher than placebo and control trials, although ratings for placebo and control trials did not differ. n.s., $P > .12$ (not significant); †$P < .12$; *$P < .05$; ***$P \leq .001$. Abbreviation: SEM, standard error of the mean.

medium ($F_{1,19} = 24.89$, $P < .001$, $\eta_p^2 = .57$, Fig 7A) pain stimuli.

In the test phase of experiment 2b, affective pain ratings varied across the 3 different conditions ($F_{2,38} = 13.79$, $P < .001$, $\eta_p^2 = .42$, Fig 7B). Pain stimuli in nocebo trials were rated as more unpleasant than in placebo trials ($F_{1,19} = 19.61$, $P < .001$, $\eta_p^2 = .51$), and in control trials ($F_{1,19} = 17.58$, $P < .001$, $\eta_p^2 = .48$). Pain stimuli in placebo trials were rated similar to those during control trials ($F_{1,19} = 0.74$, $P = .40$, $\eta_p^2 = .04$). Nocebo > control difference scores (M = 6.79; SD = 7.24) were significantly higher compared with control > placebo difference scores (M = −1.06; SD = 5.50, $t_{19} = 3.06$, $P = .007$). Sensory pain ratings also varied across the different conditions ($F_{2,38} = 13.79$, $P < .001$, $\eta_p^2 = .42$). Stimuli in nocebo trials were rated more intense than in placebo trials ($F_{1,19} = 10.57$, $P = .004$, $\eta_p^2 = .36$), and significantly more intense compared with pain stimuli in control trials ($F_{1,19} = 19.19$, $P < .001$, $\eta_p^2 = .50$). Pain stimuli in placebo trials were rated similar to pain stimuli in control trials ($F_{1,19} = 1.91$, $P = .18$, $\eta_p^2 = .09$, Fig 7B). Nocebo > control difference scores (M = 6.31; SD = 6.44) were significantly higher compared with control > placebo difference scores (M = −1.62; SD = 5.25, $t_{19} = 3.61$, $P = .002$).

No significant effect of time ($F_{1,19} = 2.89$, $P = .11$, $\eta_p^2 = .13$) or an interaction of time and condition ($F_{2,38} = 0.76$, $P = .93$, $\eta_p^2 = .004$) was detected. There was no significant correlation between pain ratings of the conditioning phase and the test phase. Taken together, the behavioral results from experiment 2a and b replicate the findings from experiment 1 and suggest that the manipulation of expectation together with experience induces stronger nocebo than placebo effects.

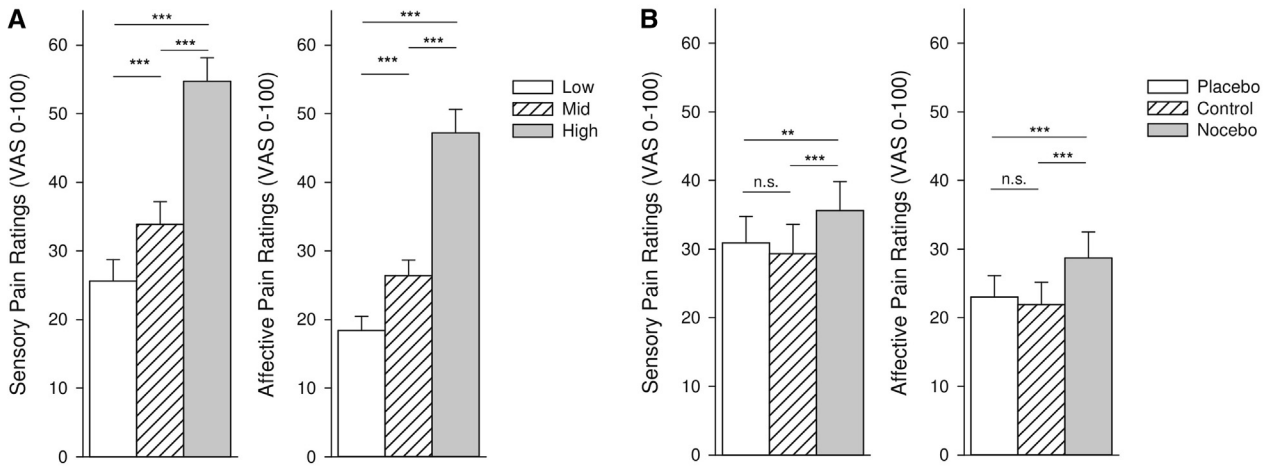

Figure 7. Experiment 2 b: Mean (±SEM) sensory and affective pain ratings are depicted for each experimental condition. In the conditioning phase **(A)** pain ratings significantly differentiated between low, medium, and high pain stimuli. In the test phase **(B)** sensory and affective pain ratings for nocebo trials were rated higher than placebo and control trials, although ratings for placebo and control trials did not differ. n.s., $P > .10$ (not significant); **$P < .01$; ***$P < .001$. Abbreviation: SEM, standard error of the mean.

Conclusions

The present study showed a significant placebo and nocebo effect on pain that resulted from a purely psychological placebo–nocebo manipulation. Importantly, this effect was only observed when both expectation and experience were manipulated as indicated by significant differences for affective—and to lesser degree for sensory—pain ratings and higher SCRs in the early nocebo compared with placebo trials in the expectation + experience group (experiment 1). These findings suggest an overadditive interaction of experience and expectancy, which is most likely a result of reinforced expectations.

Similarly, pain ratings of the acquisition and the test phase revealed only for the combination of expectation and experience a significant relationship, which suggests a potential transfer of the initial learning experience to the subsequent placebo–nocebo response. However, this correlation was weaker and only partially replicated for affective pain ratings in experiment 2a, when 3 visual cues were introduced. In experiment 1, the effect of a single placebo–nocebo instruction (expectation) was rather small, but still more pronounced than a conditioning procedure (experience), which did not result in any differences of pain perception between placebo and nocebo trials during the test phase. Although the present placebo–nocebo agent was admittedly abstract and novel to all participants, they anticipated a pain modulatory influence of the different visual patterns as indicated by the expectancy ratings of experiment 2a. Finally, pain ratings of experiment 2a and especially 2b suggest that nocebo effects can be more easily induced by a purely psychological placebo and nocebo manipulation, as revealed by a stronger differentiation between nocebo and control trials compared with placebo and control trials. The present results are in line with earlier findings that showed no or rather weak conditioned placebo responses when no further placebo instruction suggestive of analgesia was given.[1,27,39] Placebo conditioning paradigms so far mostly provided a physical, medicinal agent (eg, creams or pills) as a conditioned stimulus, which might be much more easily associated with the modulation of pain than a simple visual stimulus. Consequently, the repeated pairing of totally pain-unrelated visual cues with different levels of thermal pain might result in smaller conditioned placebo–nocebo responses and thus only small alterations of pain processing during a test phase. Therefore, a psychological placebo paradigm presumably depends on additional cognitive support such as a placebo instruction. However, just recently Jensen et al[20] induced placebo hypoalgesia by applying a behavioral conditioning procedure without any further verbal suggestions. They presented neutral faces together with either higher (nocebo) or lower (placebo) pain stimuli which led to a corresponding modulation of pain ratings when the actual pain stimulation was identical during a test phase and persisted even when the cue presentation was subliminal.[20] Contrary to the experiment by Jensen et al, the conditioning phase of the present study was shorter and placebo and nocebo cues were less salient (stripes vs faces). Further, we did not include so-called booster trials during the test phase in which placebo and nocebo cues were paired with the original pain intensity (level of the unconditioned stimulus) from the conditioning phase to prevent early extinction. Nevertheless, the results of the placebo conditioning phase and the recalled pain ratings showed that the participants in the experience group actually learned the contingency of cue and pain stimulation but failed to generalize during the test phase. One might assume that in placebo and nocebo conditioning, besides the length of the conditioning phase[13] and the reinforcement pattern,[20] the associability of the conditioned reaction to the placebo and nocebo procedure or cue is a crucial feature that influenced the magnitude of the resultant placebo response. In favor of this view, in a recent review[3] the necessity to actually attribute a pain-decreasing effect to a distinct (placebo) treatment for the successful induction of placebo responses was underscored, as was the case in the combined expectation + experience group of the present study. Furthermore, Atlas and Wager put forward a conceptual distinction between placebo paradigms that provide a placebo agent or sham treatment and experimental designs that simply evoke varying outcome expectations, for instance when cues predict high or low pain stimulation.[3] In the present study, the manipulation of expectation alone resulted only in a small modulation of pain. However, in previous experiments, placebo effects were induced only by verbal suggestion,[39] and nocebo responses were elicited even after a single announcement of the likely occurrence of negative symptoms[13] or when a participant was led to believe that the administration of an analgesic drug administration had been stopped.[7] The method of instruction of a placebo treatment was shown to affect its final outcome: Uncertain compared with certain expectations were found to induce smaller placebo responses.[33] It is noteworthy that nearly all of the studies reviewed so far provided a placebo instruction that was pharmacologically intuitive. In the present study, instead, a short and rather abstract written instruction was given, which alone did not suffice to induce a significant placebo–nocebo response during the test phase. However, when the predictions about the pain-modifying properties of the visual black and white stripe patterns were reassured during placebo–nocebo conditioning (expectation + experience), a significant placebo–nocebo differentiation was elicited on the behavioral and on the physiological levels. These results fit very well with previous findings that showed the strongest placebo effect for the combination of placebo instruction and conditioning[13,25,39] and suggest that expectation and actual experience interact in an overadditive manner, mutually reinforcing each other.

In contrast to earlier findings, the placebo–nocebo agent of the present study consisted of a purely psychological, nonpharmacologically driven procedure. This potentially provided lower levels of persuasiveness and therefore resulted in less pronounced differences as shown by the results of the expectation group. The

results suggest that when rather weak placebo–nocebo instructions are provided, it is necessary to confirm their effectiveness and potency with an actual experience. By introducing an additional neutral control condition, experiment 2a and especially 2b showed that a psychological placebo–nocebo manipulation evoked predominantly nocebo responses, as shown by the more pronounced differences between nocebo and control trials than between placebo and control trials. This supports earlier findings that showed that nocebo effects might be achieved more rapidly than placebo effects[13] because they rely on shorter learning periods and subsequently persist longer in time.[29] Interestingly, in experiment 2b, in which the medium temperature of the control condition during the conditioning phase served as the test temperature, the ratings for the control condition seemed to decrease during the test compared with the conditioning phase. Instead, in experiments 1 and 2a, ratings of nocebo trials (which were always at the same, high-temperature level) seemed to increase during the test compared with the conditioning phase. This showed that methodological differences (such as the temperature level of test stimuli and the conditioning procedure) should be carefully taken into account in comparisons of results of different experiments. Also, temporal dynamics of placebo and nocebo effects should be addressed more thoroughly. Regarding the present design, we assumed that comparisons of different experimental conditions at similar time points might be the least biased approach.

In a recent model on the generation of placebo hypoalgesia it was proposed that the placebo response is the result of a recurrent integration of bottom-up information (ie, sensory, nociceptive input) and top-down processes (ie, previous experiences and expectations).[8] According to the model, the magnitude of the placebo response relied on the certainty that a (placebo) treatment would actually be administered and the expectation regarding the potency of the treatment, which is, in part, the result of previous experiences. In line with this view, it was shown that treatment history has an immense effect on future treatment outcome, such that a positive placebo experience promoted the placebo response in a follow-up session and even could be transferred to a different placebo agent.[23] In general, the treatment history was discussed to shape the individual attitude toward medical interventions, to moderate the actual treatment outcome, and to affect placebo and nocebo responses.[6,16,24] Consequently, placebo paradigms that are unfamiliar to a participant are necessary and thus allow circumvention of any confounding factors that might arise because of the resemblance to earlier treatments when expectation and experience are meant to be kept apart. Therefore, the present design provided an ideal paradigm to further disentangle mechanisms that constitute placebo and nocebo effects. Future studies might elaborate methodological issues of placebo and nocebo effects on the basis of the considerations that motivated the present study. For instance, it was shown that an intensive, procedural therapy resulted in stronger effects than the administration of a pill alone.[21] Similarly, a neuromodulator like oxytocin was found to support the feeling of trustworthiness and hence placebo analgesia.[22] These findings might be replicated in circumstances in which the applied agent is not familiar to the participants and therefore a reference to earlier medical treatments is less salient. Probably the most ambitious challenge will represent the surreptitious substitution of "real" agents with psychological placebos, following the logic of placebo-controlled dose reduction[15] when the administration of a drug is initially combined and later on completely replaced by a placebo treatment, saving resources and reducing physiological side effects. In addition, future studies in clinical samples should evaluate whether pain modulatory placebo and nocebo mechanisms resemble those in healthy control subjects. Some investigators have shown that in patient samples, the placebo effect serves to reduce hyperalgesia or pathologically altered pain responses.[29,30] This might be a very different process than the typical analgesic or hypoalgesic response seen in asymptomatic individuals. Most important, upcoming experiments will need to sensitively evaluate the individual treatment history and investigate its effect on treatment outcome and placebo and nocebo responses.

Several limitations need to be considered in interpretation of the results of the present study. The experimental paradigm of experiment 1 was best suited to investigate placebo effects because the temperature during the test phase was identical to the nocebo temperature of the conditioning phase. To maximize contrasts between conditions, we chose to instruct opposing effects (pain augmentation vs pain relief), which might lead to placebo versus nocebo expectations, respectively. We therefore referred to the resulting pain modulation as a placebo–nocebo effect. Furthermore, in experiment 1 the successful induction of expectations could only be assumed indirectly according to the recalled pain ratings of the expectation group. This assumption was also supported by a priori expectancy ratings of experiment 2 (Fig 5), which comprised a very similar manipulation. However, explicit expectation ratings would have been informative to more precisely disentangle the involved processes.

Regarding the results of experiment 1, smaller differences in sensory compared with affective pain ratings might have been because of the wording of verbal anchors for the sensory and affective pain VAS: The upper end point of the sensory VAS "unbearable pain" (sensory pain component) likely did not match the corresponding end point of the affective VAS "extremely unpleasant" (affective pain component) and therefore might have lead to a different range within the ratings. However, the results of all 3 experiments did not show systematic differences for sensory and affective pain ratings.

The results of experiment 2b suggest increased nocebo responses, but it cannot be excluded that this effect was partially driven by an already more pronounced perceived difference between nocebo and control trials during conditioning. Such an alternative explanation could be potentially circumvented by psychophysically

calibrated pain stimulation levels, which take into account the nonlinearity of heat pain perception.[28] Differences in magnitude of (purely psychological) placebo and nocebo effects demand additional research and replication; similarly, the successful induction especially of placebo analgesia by psychological means should be further addressed in future studies. In experiment 1, SCR results revealed a significant modulation by placebo and nocebo conditions only in the beginning of the test phase. This indicated that physiological effects were rather short-lasting and restricted to the paradigm in which only 2 conditions were compared.

In summary, the present study showed that it is possible to induce alterations of pain perception by a purely psychological placebo–nocebo manipulation that does not rely on any earlier associative learning experiences such as past medical treatments. The results showed an overadditive interaction of a suggestion-induced expectation and its subsequent affirmation through classical conditioning, which were sufficient to change physiological responses and behavioral measures of pain. Moreover, our results point to the importance of a combination of expectation and experience when the introduced pain modulatory mechanism is psychological and hence less conventional. Obviously, exploiting placebo effects is a crucial feature of medical practice; however, as previous and our current results show, the efficient prevention of nocebo effects might be at least equally important. Overall, the presented placebo–nocebo paradigm provided a promising avenue for further research on the psychological foundations of placebo and nocebo effects.

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