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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