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Original Reports

Conditioned Placebo Analgesia Persists When Subjects Know They Are Receiving a Placebo

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Abstract: Belief in the effectiveness of a placebo treatment is widely thought to be critical for placebo analgesia. Many types of placebo responses—even those that depend on conditioning—appear to be mediated by expectations that are strengthened as treatment cues are reinforced with positive outcomes. However, placebo effects may occur even when participants are aware they are receiving a placebo. To address the question of whether conditioned placebo analgesia can persist in the absence of expectations, we studied the effects of long (4 days) versus short (1 day) conditioning to a placebo treatment. After an initial placebo test, a "reveal" manipulation convincingly demonstrated to participants that they had never received an active drug. Placebo analgesia persisted after the reveal in the long conditioning group only. These findings suggest that reinforcing treatment cues with positive outcomes can create placebo effects that are independent of reported expectations for pain relief.

***Perspective:** This article demonstrates a form of placebo analgesia that relies on prior conditioning rather than current expected pain relief. This highlights the importance of prior experience on pain relief and offers insight into the variability of placebo effects across individuals.*

***Key words:** Placebo, pain, conditioning, expectancy, reversal.*

Placebo analgesia is pain relief observed following administration of a treatment that is not directly caused by pharmacological properties of that treatment. Placebo analgesia is typically induced in the laboratory using a "response conditioning" paradigm, where treatment cues (eg, a cream or injection) are paired with surreptitious reductions in the intensity of painful stimuli.[25,33] Afterward, painful stimuli are presented under placebo (paired) and control (unpaired) conditions to test for placebo effects. This procedure is a model paradigm in the study of placebo analgesia and the influence of expectations on pain and other affective, perceptual, and physiological processes.[24,31,35]

Early studies concluded that the experience of pain relief was critical for reliably inducing placebo analgesia,[33,34] but it is now generally understood that placebo analgesia is directly mediated by expectations and only indirectly relies on prior experiences.[2,6,19,21,24] Manipulations of expectations produce pain relief,[2,7] and greater expectancies are associated with greater placebo analgesia.[18,21,22,25,37] Even within conditioning paradigms, expectancies appear to be critical: When subjects attribute pain relief to sources other than a placebo treatment, they do not acquire placebo analgesia,[21,38] and verbal suggestions of hyperalgesia can block conditioned placebo analgesic effects.[6,7,14]

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These findings fit within a broader literature suggesting that conditioning depends on the information value of cues rather than associative pairing per se[26] and may reflect inferential rather that gradual learning processes.[12]

Expectancy theory implies that belief in the placebo is critical for placebo analgesia. This expectation need not be a belief in the chemical analgesic properties of the treatment but may instead be a more general belief that a placebo treatment can relieve symptoms. This belief may allow placebos to serve as either dose extenders for chemically active treatments[28,29] or effective treatments on their own.[17] However, expectancy theory is challenged by demonstrations that placebo treatments can result in analgesia even when participants are unaware they are receiving a treatment.[2,15] Other placebo manipulations that generate expectancy-independent placebo effects (eg, conditioned immunosuppression) generally use multiple conditioning sessions,[1,6] and increasing the number of conditioning sessions leads to placebo analgesia that is both stronger and more resistant to extinction.[10] A key question is whether enhanced placebo analgesia following multiple conditioning sessions also depends on expectancy. If not, this suggests the existence of a class of placebo analgesia that depends on conditioned associations[3] and, like conditioned immunosuppression, is independent of expectations. These placebo effects should depend on the duration of conditioning, be independent of reported expectations, and persist when expectations are reversed.

In order to determine whether conditioned placebo analgesia persists when subjects are made aware of a placebo treatment, pain response was tested both before and after a complete and convincing disclosure of the placebo manipulation (placebo reveal). To directly measure the role of associative learning in "open-label" placebo effects, we varied the number of conditioning sessions and tested whether postreveal placebo effects were greater for participants who had experienced more conditioning sessions. Critically, we measured expected pain relief both before and after the placebo reveal, as nonconscious cues may continue to elicit expectations for pain relief.[15] We hypothesized that participants who experienced more conditioning would engage mechanisms for placebo analgesia that were independent of reported expectancies and would continue to show placebo analgesia even when aware that the treatment was a placebo.

Methods

Participants

Fifty-four participants (30 female, ages 18–55) were recruited via online advertisements on a recruitment website managed by the School of Medicine at the University of Colorado Anschutz Medical Campus. Data collection was planned to continue until 40 participants met inclusion criteria and completed the study. Twelve participants were excluded during an initial calibration because they did not find the thermal stimuli sufficiently painful (average pain rating below 30 on a 100-point visual analog scale [VAS] for a 48°C stimulus), and 2 participants stopped participation midway through the study because of discomfort from the heat. It was also required that participants' pain ratings increase with higher stimulation temperatures during the initial calibration ($R^2 > .40$), but no participants were excluded on the basis of low temperature discriminability. A total of 40 participants were included in the final analysis, 20 in the long conditioning group (long; 13 female participants) and 20 in the short conditioning group (short; 14 female participants). All participants gave informed consent to participate in a study of treatment effects on pain relief and were fully debriefed at the conclusion of the study. This study was approved by the University of Colorado Boulder Institutional Review Board.

Materials and Procedures

Overview

Participants were informed that they were participating in a study to compare the analgesic effects of a topical cream containing an active analgesic component (placebo cream) to those of a topical cream containing no active ingredients (control cream). Following the initial calibration phase, subjects were randomized to long or short conditioning groups and began the conditioning phase of the study. Immediately following

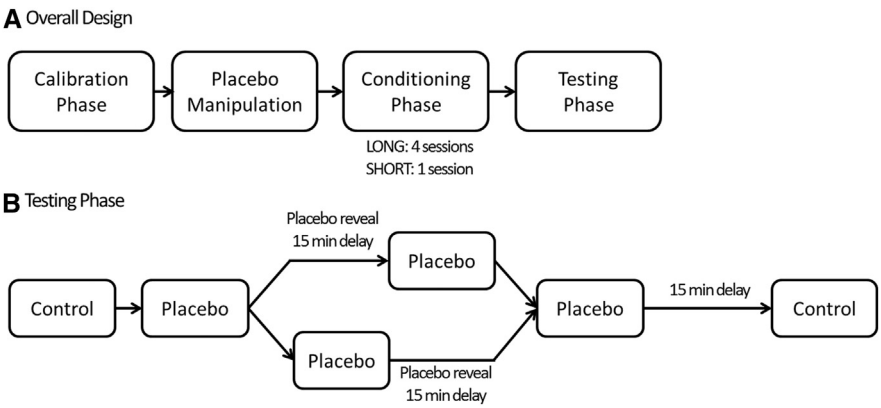

Figure 1. Study design. **(A)** Participants in the long group had 4 sessions during the conditioning phase and participants in the short group had a single session. **(B)** During the testing phase, the placebo reveal occurred after the first placebo run for half of all subjects and after the second placebo run for the remaining subjects.