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Expectancy and Conditioning in Placebo Analgesia: Separate or Connected Processes?

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Abstract

Expectancy and conditioning are often tested as opposing explanations of placebo analgesia, most commonly by pitting the effects of a conditioning procedure against those of a verbally-induced expectation for pain reduction. However, conditioning procedures can also alter expectations, such that the effect of conditioning on pain might be mediated by expectancy. We assessed the effect of conditioning on expected pain and placebo-induced pain reduction. Participants were told that the treatment (real or sham acupuncture) would affect one side of the arm but not the other. Because a real acupuncture effect would not be specific to a randomly selected side of the arm, any difference in pain between the “treated” and the “untreated” side would be a placebo effect. There were no significant main effects or interactions associated with type of acupuncture (real versus sham). In both groups, conditioning decreased expected pain for “treated” location and also increased the placebo effect (i.e., the difference in pain report between “treated” and “untreated” locations). In addition, mediation analysis lent support to the hypothesis that the effects of conditioning on placebo analgesia may be mediated by expectancy, although the size of this indirect effect requires further study.

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Expectancy and conditioning are widely considered the primary explanatory models of placebo effects (Colloca & Miller, 2011; Stewart-Williams & Podd, 2004). Often, they are tested as opposing explanations, most commonly by pitting the effects of a conditioning procedure against those of a verbally-induced expectation (e.g., Colloca, Sigaudo, & Benedetti, 2008; Klinger, Soost, Flor, & Worm, 2007; Klosterhalfen et al., 2009; Voudouris, Peck, & Coleman, 1990). The results of these studies indicate that conditioning produces a greater placebo analgesic response than verbally induced expectancies.

These tests implicitly assume that conditioning and expectancy are independent mechanisms. An alternative perspective suggests that conditioning and verbal information are two different means of inducing and altering expectations (Colloca & Miller, 2011; Kirsch, 1985; Montgomery & Kirsch, 1997). From this perspective, expectancies can be produced by verbal information, direct experience (conditioning), social observation (modeling), or other sources of information. Therefore, expectancies are hypothesized to mediate the effect of these procedures on placebo effects.

To test the hypothesis that expectancy mediates the effect of conditioning on placebo analgesia, we performed analyses on the behavioral results from a previously published fMRI study, in which a conditioning procedure was used to induce placebo effects on pain perception and its effects on both expected and perceived pain were assessed (Kong et al., 2009a; Kong et al., 2009b). The placebo in this study was sham acupuncture. The conditioning procedure involved surreptitious reduction of stimulus intensity on a “treated” part of the body, but not on an “untreated” location of the right forearem, following which, the initial stimulus intensity was restored and the placebo effect was assessed. These procedures were first developed by Voudouris and colleagues (Voudouris, Peck, & Coleman, 1985) and have been used in many fMRI studies of placebo analgesia (e.g., Kong et al., 2008; Kong et al., 2013; Kong et al., 2006; Wager et al., 2004). In this new analysis, we compared the effects of this procedure against those of a control condition, in which the stimulus intensity was not reduced in the conditioning phase. As in prior studies of conditioned analgesia (e.g., Colloca, et al., 2008; Klinger, et al., 2007; Klosterhalfen, et al., 2009; Voudouris, et al., 1990), participants in the control groups received the same verbal information as those in the conditioning group about the pain reducing potential of the treatment, but without the experience of surreptitiously reduced pain.

Our study included a verum acupuncture group as well as a sham acupuncture group. Participants in both groups were misinformed that the acupuncture treatment would affect one side of their arm but not the other. Because a genuine acupuncture effect would not be specific to a randomly selected side of the arm, any difference in pain between the “treated” and the “untreated” side would be a placebo effect. Placebo effects are components of active treatment, capable of enhancing the response to treatment (Benedetti, Maggi, et al., 2003; Colloca, Lopiano, Lanotte, & Benedetti, 2004). Hence, our design allowed us to test for conditioned and unconditioned placebo effects in both sham and verum acupuncture.

To allow evaluation of the hypothesis that the effect of the conditioning manipulation was mediated by expectancy, we assessed treatment related expectancies for pain reduction, as well as changes in perceived pain. These data were analyzed using recommended procedures

for assessing mediation (MacKinnon et al., 2002; Shrout & Bolger, 2002; Woody, 2011). Specifically, if the effects of conditioning procedures on pain are mediated by expectancy, then (a) conditioning (vs. control) should predict expectancy, (b) when conditioning is controlled, expectancy should predict placebo analgesia; and (c) the product of these foregoing two effects, which represents the expectancy-mediated indirect effect of conditioning on the placebo effect, should be statistically significant.

Methods

Participants

Participants were 24 male and 24 female healthy volunteers (mean age 26.4 years ± 4.9 SD) who were naïve to acupuncture. Experiments were conducted with the understanding and written consent of each participant and approval by the Human Subjects Committee at Massachusetts General Hospital. At the end of the experiment, all the participants were told about the true nature of the experiment and its methods as they had been recruited with the understanding that this was a study about acupuncture analgesia, and were not informed about the surreptitiously lowered temperatures or the use of sham needles.

Design

We used a 2×2×2 (verum vs. sham acupuncture by conditioning vs. control by pre vs. post) mixed model design. Participants were randomized to receive either verum or sham acupuncture treatment and to receive or not receive surreptitiously reduced pain stimulation during conditioning trials. In addition, pain was assessed on both the radial and ulnar sides of the ventral forearm, and participants were misinformed that the acupuncture treatment would affect only one side of the arm.

Assessment of Noxious Thermal Stimuli

Calibrated thermal pain stimuli were delivered to the right ventral forearm using a TSA-2001 Thermal Sensory Analyzer with a 3 cm × 3 cm probe (Medoc Advanced Medical Systems, Rimat Yishai, Israel) running proprietary computerized visual analog scale software (COVAS). Each stimulus was initiated from a 32°C baseline, increased to a target temperature, and presented for 12 seconds, including 2.5 second ramp up and ramp down. Inter-stimulus interval ranged from 24–30 seconds. During that interval, participants were given the task of assigning a numerical rating value to the pain and to press a button that moved a cursor to indicate that value.

Stimuli were administered in blocks of six trials each. To improve the consistency of pain administration in Sessions 2 and 3, we used a marker to draw a numbered 2 × 3 grid on the ventral aspect (palmar side) of the right forearm to create distal to proximal rows of 3 boxes each on the “treated” and “untreated” sides. We placed the thermal probe in one box of the grid for each of the stimuli sequences. Between each block of trials, the thermal probe was physically moved to a new location on the grid. This assured that each stimulus for each block of trials was far enough apart to activate a different population of sensory afferent fibers, thereby minimizing sensitization or habituation effects. The time interval between blocks of trials was approximately 5 minutes.

Pain was rated on a 0–20 Sensory Box scale (Gracely, McGrath, & Dubner, 1978a, 1978b). Internal consistency across the 12 trials in each condition was assessed by Cronbach's alpha. These data indicated that pain ratings were very extremely reliable in all conditions (Pre-treatment Told Treated, alpha = .94; Pre-treatment Told Untreated, alpha = .94; Post-treatment Told Treated, alpha = .95; Post-treatment Told Untreated, alpha = .95). The placebo effect was defined as the difference in pain ratings for the "treated" location and pain ratings for the "untreated" side.

A 0–20 Sensory Box scale was also used to measure expectations. This was identical in format to the Sensory Box scale, except that participants were asked to rate how intense they thought the pain would be after acupuncture treatment on both the "treated" and "untreated" sides. We assessed test-retest reliability by administering the expected pain measure at the end of Session 2 and again at the beginning of Session 3. This resulted in test-retest correlations of $r = .90$ for the "treated" side and $r = .94$ for the "untreated" side. The expected treatment effect was calculated as the difference between expected pain for the "treated" side and expected pain for the "untreated" side. The data for one participant in the conditioning group, who neglected to complete the expectancy ratings, was removed from the analyses.

Session 1

Participants were recruited to participate in three sessions, each of which was separated by a minimum of four days. We used the first session to determine appropriate stimulus intensities for each participant, to minimize anticipatory anxiety, to control for rating strategy and learning effects, and to teach the participants to rate the stimuli using the Sensory Box and Affective Box 0–20 scales (Gracely, et al., 1978a, 1978b). This session consisted of two phases: ascending series and random sequence.

Participants first experienced an ascending series of calibrated heat stimuli (the first stimulus was increased from the baseline of 32°C to a target of 38°C and the target temperatures for the following stimuli increased by 1°C to the participants' tolerance or to a maximum of 52°C) on both arms. Temperatures that elicited subjective intensity ratings in the LOW pain range (8–11; the mild to moderate range on the 0–20 Sensory Box Scale) and HIGH pain range (14–17; the strong to intense range on the 0–20 Sensory Box Scale) were selected for each participant.

Then we applied a random sequence of HIGH and LOW intensity stimuli, in which the two intensity levels were each presented to the right arm an equal number of times in a random order. Temperatures were adjusted when necessary to ensure that subjective ratings of the temperature established for that participant as HIGH or LOW were in the desired range. By the end of this session, HIGH and LOW intensities (temperatures) were determined and these temperatures were used in the subsequent sessions. The random sequence provided a way to determine how reliably a participant could rate noxious stimuli of different intensities when they were presented in an unpredictable order.

Session 2

The second session was designed to detect if participants could reliably rate calibrated noxious heat stimuli and to produce a conditioned placebo response in the conditioning groups, using a method modified from previous work (Kong, et al., 2008; Kong, et al., 2006; Montgomery & Kirsch, 1997; Price, et al., 1999; Wager, et al., 2004). The session consisted of four phases: 1) random sequences of high and low intensity pain stimuli, 2) pre-treatment fixed sequences of pain stimulation, 3) verum or sham acupuncture, and 4) post-treatment expectancy manipulation. The conditioning procedure consisted of the repeated application of a fixed sequence of pain stimulation, with surreptitiously lowered temperatures for participants on the "treated" side. In this session, participants also twice completed the expected pain scale form (once before treatment and once at the very end of the session) indicating how intense they expected the pain to be after acupuncture treatment.

At the beginning of Session 2, participants were told that responses to acupuncture can be positive or neutral, and that a person's response tends to remain consistent across sessions. Participants then viewed a traditional Chinese medicine meridian diagram and were told that acupuncture could only produce analgesia on the side of the arm through which the meridian passed (the "treated" side, where the needles would be placed) but not on the other side of the arm (the "untreated" side). Half the participants were shown accurate diagrams (real diagram) of the LI Meridian passing through the radial side of the arm, while the other half viewed a modified diagram (fake diagram), showing the LI Meridian passing through the ulnar side of the arm.

Next random sequences of HIGH and LOW pain stimulation were administered to the bottom two boxes on the 2×3 grid and fixed sequences were applied to the top four. To proceed in the study, participants had to consistently rate HIGH pain greater than LOW pain, and report approximately equivalent ratings to fixed sequence MODERATE pain on the radial and ulnar sides of their arm.

In fixed sequence, from which pre-treatment pain assessments were derived, we applied six stimuli set at an intensity level halfway between HIGH and LOW. For example, a participant who received 47 °C for LOW and 50 °C for HIGH stimuli would have a stimulus temperature in the fixed sequence of 48.5 °C. The consistency in the fixed sequence enabled us to better manipulate participants' expectancy of acupuncture analgesia by providing a way for participants to easily compare stimulus intensity before and after treatment.

Sham Acupuncture and Verum Acupuncture administration

After pre-treatment assessment, we administered a verum or sham electro acupuncture treatment to one side of the arm. As noted above, participants were randomized into two groups so that either the radial (LI) or ulnar (SI) side of the forearm became the "treated" or "untreated" side. Sham or verum acupuncture was performed at Large Intestine 3 and 4 (LI 3 & 4) on the right hand by a licensed acupuncturist. For sham electro acupuncture, specially designed Streitberger sham acupuncture needles were placed on the surface of the skin and connected to a de-activated electro acupuncture device. This placebo needle retracts into its handle when pressed on the skin, similar to the action of a retractable stage knife. The

Streitberger needle has been validated and used in many studies (Kleinhenz et al., 1999; Kong et al., 2005; Kong, et al., 2006; McManus et al., 2007; Streitberger & Kleinhenz, 1998; White, Lewith, Hopwood, & Prescott, 2003). For verum electro acupuncture, needles were adjusted until *deqi* but no sharp pain, was evoked. Needles were then connected to an electro acupuncture device passing a 2 Hz current (OMS Medical Supplies IC-1107) (Kong, et al., 2005). In total, sham and verum acupuncture lasted approximately 25 minutes. Verum treatments were further broken down into three 6.5-minute (current ON), 1.5-minute (current OFF) blocks.

Conditioning

After the acupuncture or sham treatment, we told the participants that we would administer the same pre-treatment stimuli to test the analgesic effect of acupuncture. In actuality, we repeated the pre-treatment fixed sequences on both meridian and non-meridian side only in no-conditioning groups. In the conditioning groups, we surreptitiously decreased the temperature of all noxious stimuli by 4–6 °C on the "treated" side, but used the same stimuli temperature as before on the "untreated" side. A reduction of this magnitude on the "treated" side should elicit a rating of "faint to weak" (1–5 on the Gracely Sensory Box scale) and was designed to give participants an unmistakable experience of profound analgesia in both fixed and random stimuli sequences. On the "untreated" (control) side, the temperatures remained at pre-treatment HIGH levels to further impress the "good effect" of acupuncture treatment. This procedure mirrored a conditioning model in which some areas of the arm receive a placebo analgesia cream while adjacent areas act as a control (De Pascalis, Chiaradia, & Carotenuto, 2002; Kong, et al., 2006; Montgomery & Kirsch, 1997; Price, et al., 1999; Voudouris, et al., 1990; Wager, et al., 2004; Watson, El-Deredy, Bentley, Vogt, & Jones, 2006; Watson, El-Deredy, Vogt, & Jones, 2007). As in previous studies, the control group experienced the same number of stimuli, but without the temperature reduction. To the extent that the baseline placebo effect is due to prior conditioning, this may be regarded as an extinction control group. It is distinctly different from a nocebo conditioning procedure, in which the temperature is increased on the "treated" side (e.g., Kong, et al., 2008).

Session 3

Session 3 was performed in an fMRI scanner, and participants were told we would repeat the procedures of Session 2. First, participants completed the expectation scale. Then they got the 2 × 3 grid marked on their forearm. Then received two random sequences in the most distal boxes and the four fixed stimuli sequences in the remaining boxes. Then they received verum or sham acupuncture treatment on the same "treated" side as they had in Session 2.

After treatment, participants were told that we would again present the same stimuli sequences to test the acupuncture analgesia effect. As in Session 2, we decreased stimulus temperature on the "treated" side for the conditioning group. We intended for this to act as a boost to further reinforce the conditioned placebo response. In the no-conditioning control groups, intensity levels were not reduced on the "untreated" side. The expectation scale was then re-administered, following which fixed stimuli sequences were delivered at the original stimulus temperature on both "treated" and "untreated" sides to test for an analgesia effect evoked by treatment.

Results

Using SPSS 20.0 (Chicago, IL, USA), the effect of conditioning and acupuncture on the placebo effect (i.e., pain on the "untreated" side – pain on the "treated" side) was analyzed in a 2×2×2 (conditioning by acupuncture by pre-post) mixed model analysis of variance (ANOVA). Acupuncture (verum vs. sham) was included in these analyses to check for interactions. However, even in the verum acupuncture group, we were assessing the placebo effect, because an acupuncture effect would not have been specific to one side (i.e., the side on which they were told the treatment would be effective).

There were no significant main effects or interactions associated with verum vs. sham acupuncture. Therefore results are reported for both groups of participants combined.

Conditioning

Mean pain ratings on the "treated" and "untreated" sides before and after the conditioning phase are presented in Table 1. Figure 1 displays the placebo effect before and after the conditioning phase. The ANOVA revealed a significant main effect of time, F (1,44) = 16.73, $p < .001$, with the placebo effect being greater after the conditioning phase than before it. There was also a significant interaction between time and conditioning, F (1,44) 10.86= , $p <.002$). Within group t-tests indicated that the post-conditioning phase increase in the placebo effect was significant for participants in the conditioning group (p = .0002), but not for those in the control group (p = .45).

Expectancy Mediation

There are several ways to evaluate the hypothesis of mediation, and recent work suggests that they typically yield reasonably consistent conclusions (Hayes & Scharkow, 2013). Using Amos 20 (Arbuckle, 2011), we estimated a model in which conditioning was allowed to have an indirect, expectancy-mediated influence on the placebo effect, and which also allowed the possibility of a direct influence of conditioning on the placebo effect. As shown in Figure 2, conditioning strongly affected expectancy, and, controlling for conditioning, expectancy significantly predicted the placebo effect. These effects accounted for substantial proportions of variance in the intermediary and outcome variables. The fact that both of these crucial paths are statistically significant yields support for the hypothesis of mediation (MacKinnon et al., 2002). In addition, the indirect effect, calculated by taking the product of these two paths, was also statistically significant according to the Sobel test, $Z = 1.98$, $p < .05$, garnering further support for expectancy as a mediator. The bias-corrected bootstrap approach yielded a somewhat less encouraging finding, with a 95% confidence interval ranging from .70 to −.17 and a p-value of .16. Bootstrapping likely resulted in somewhat different findings because there were two particularly strong responders to the conditioning, which would have generated a high degree of variability in the bootstrap samples. The relatively large confidence interval suggests that further study is needed to clarify the size of the mediated effect.

Discussion

Expectancy was manipulated verbally in this study by telling participants that acupuncture would affect only one of two sides of the forearm to which pain stimulation was applied. The difference in pain report between the “treated” and “untreated” side of the arm was the placebo effect. In addition, half of the participants experienced a conditioning procedure, in which the intensity of pain stimulation was lowered surreptitiously on the “treated” side of the arm. As in previous studies, this conditioning procedure significantly boosted the placebo effect.

The conditioning procedure has been hypothesized to directly affect pain, independently of expectancy (Voudouris, et al., 1990). Indeed, conditioning and expectancy are often portrayed as independent processes, and their effects compared by giving one group verbal information only and providing conditioning trials to another group. Others have argued that conditioning and expectancy are not independent processes. Conditioning provides an experience of an analgesic effect in association with the conditional stimulus (e.g., a placebo), and this experience is likely to influence their expectancies for pain relief. Hence, rather than being an independent process, conditioning may be a means of altering expectations (Rescorla, 1988).

Consistent with Rescorla’s conception, in our study, conditioning altered the expected placebo analgesia effect, which, in turn, altered the actual placebo effect. The proportions of variance accounted for in expectancy and the placebo effect were substantial. In addition, with expectancy controlled, the direct relation between conditioning and the placebo effect became small and statistically insignificant. Our results are consistent with previous studies of the placebo response in which expectancy has been assessed (Montgomery & Kirsch, 1997; Price, et al., 1999) and also with studies showing that verbal information can block the effect of conditioning (Benedetti, Pollo, et al., 2003; Montgomery & Kirsch, 1997; Watson, et al., 2006; Watson, et al., 2007).

The results of many previous studies purporting to pit expectancy against conditioning remain important, but they require reinterpretation. Because conditioning procedures alter expectancies, these studies cannot compare the effects of conditioning to those of expectancy. Rather, they contrast verbal information alone to conditioning, both of which may be at least partially mediated by expectancy. The direct experience produced by conditioning trials is a particularly powerful means of altering and strengthening expectations. Yet it is not the only means. Expectations can also be altered by verbal information and by modeling (i.e., the observation of others responding) (Colloca & Benedetti, 2009; Colloca & Miller, 2011).

Although our data indicate that expectancy may be an important mediator of the effect of the conditioning trials on pain perception, we do not claim that all conditioned placebo effects are expectancy mediated. For example, Benedetti and colleagues have reported convincing data indicating a conditioned placebo effect in hormonal responses that is not mediated by expectancy (Benedetti, Pollo, et al., 2003). Also, conditioning has been reported in organisms with very rudimentary nervous systems, which would be difficult to explain in

terms of expectations (Hawkins, Abrams, Carew, & Kandel, 1983). Nevertheless, placebo effects on consciously experienced response appear to be largely mediated by expectancy (Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005).

Although expectancies are typically regarded as conscious phenomena, there are data suggesting that they might also operate outside of conscious awareness. This occurs, for example, in sporting situations, where people have to react too quickly for conscious deliberation to be involved, but recent studies show the acquisition of unconscious expectancies. In one study (Dienes, Baddeley, & Jansari, 2012), participants were asked to predict whether stimuli would be presented on the left or right side of a computer screen. The presentations were random, and most participants thought they were merely guessing. Nevertheless, the statistical association between their predictions and the side on which the stimulus appeared in past trials indicated associative learning. These unconscious learned expectations seem analogous to the phenomenon of blindsight, in which behavior indicates perception while the person's phenomenology is that they are merely guessing (Marshall & Halligan, 1988). Another recent study has shown that individuals can respond to conditioned stimuli associated with increased or decreased pain stimulation even when the stimulus is presented below the threshold for conscious recognition (Jensen et al., 2012).

Data indicating that expectancies can be acquired and activated outside of consciousness suggest one of the limitations of our study. If expectancies can be activated unconsciously, as suggested by these data, then reliance on verbal report may underestimate the role of expectation in studies like ours. In addition, our study was conducted on healthy participants with no prior exposure to acupuncture. Hence there was no pre-conditioning placebo effect. The next task will be to establish whether these results can be generalized to patients with chronic pain disorders and to those with prior exposure to the active treatment being mimicked by the placebo.

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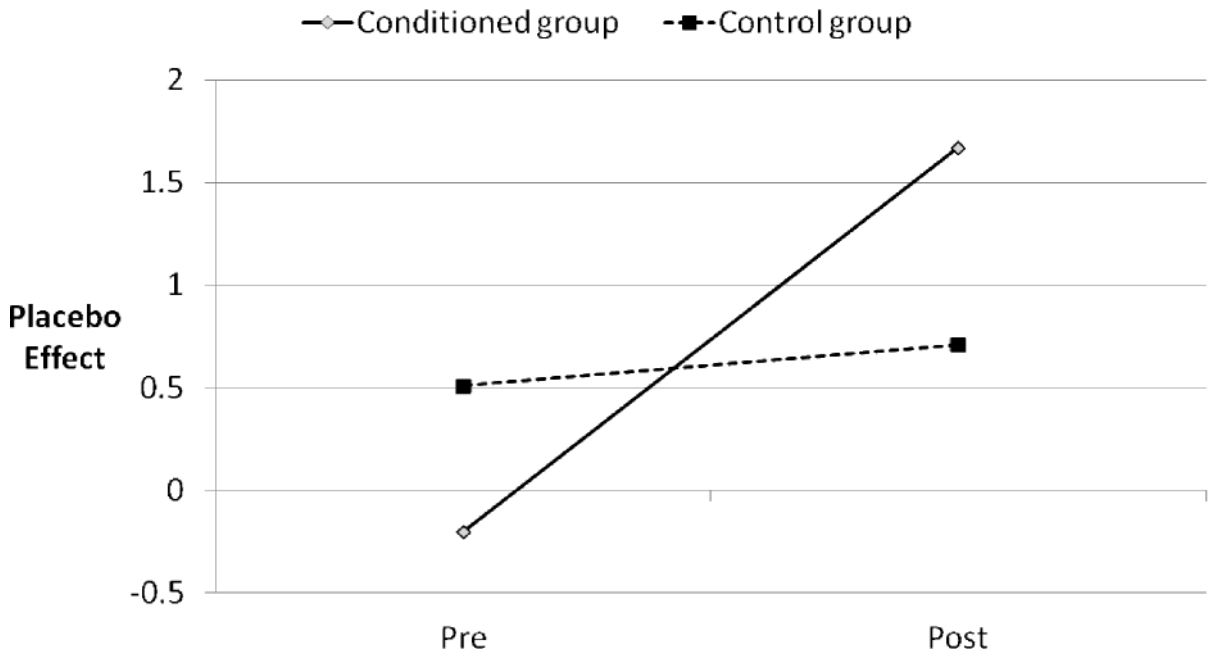

Figure 1.

The Placebo Effect Before and After the Conditioning Phase. The placebo effect is the difference in pain report between “treated” and “untreated” locations (i.e., between the location the participant was told would be affected by acupuncture treatment and the location the participant was told would not be affected by treatment).

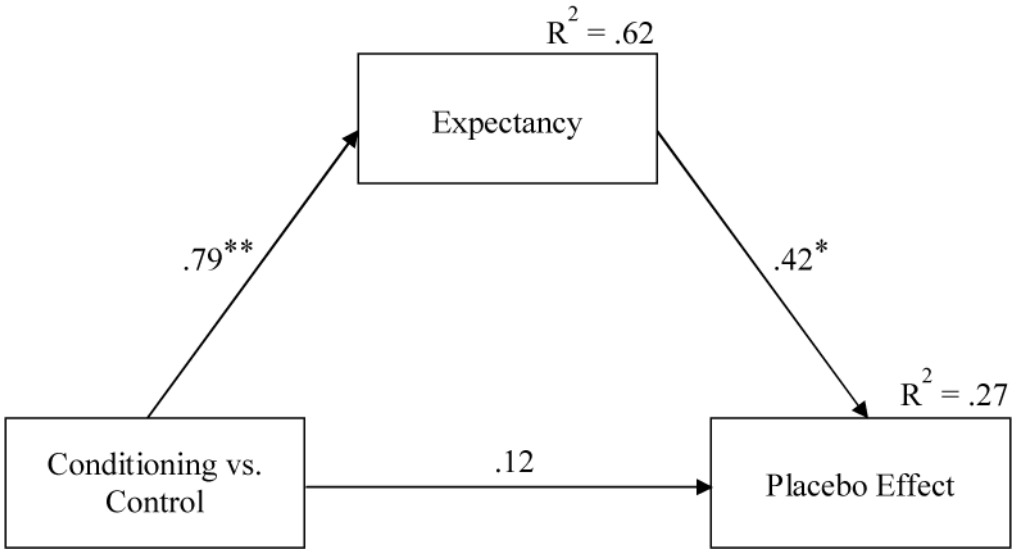

Figure 2.

Expectancy as a Mediator of the Relation Between Conditioning and the Placebo Effect. The Placebo Effect was calculated as the pain difference between the untreated and treated sides of the arm post-treatment, as compared to pre-treatment.

Note. All path coefficients are standardized and proportions of variance accounted for in the predicted variables are shown above them. * $p < .05$; ** $p < .001$.

Table 1

Mean (SD) Pain Report Before and After the Conditioning Phase on “Treated” and “Untreated” Sides

	Time	
Group	**Pre**	**Post**
Conditioned		
“Treated”	13.61 (2.28)	12.44 (2.89)
“Untreated”	13.41 (2.46)	14.10 (2.00)
Control		
“Treated”	12.61 (2.37)	12.97 (2.31)
“Untreated”	13.12 (2.35)	13.68 (2.09)